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MAY 1954
VOLUME 93 NUMBER 5

Published Monthly by
AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter Jan. 23, 1909, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $10.00

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1. Russek, H. I.; Urbach, K. F.; Doerner, A. A., and Zohman, B. L.: J.A.M.A. *153*:207 (Sept. 19) 1953.
2. Humphreys, P., *et al.*: Angiology *3*:1 (Feb.) 1952.
3. Plotz, M.: New York State J. Med. *52*:2012 (Aug. 15) 1952.

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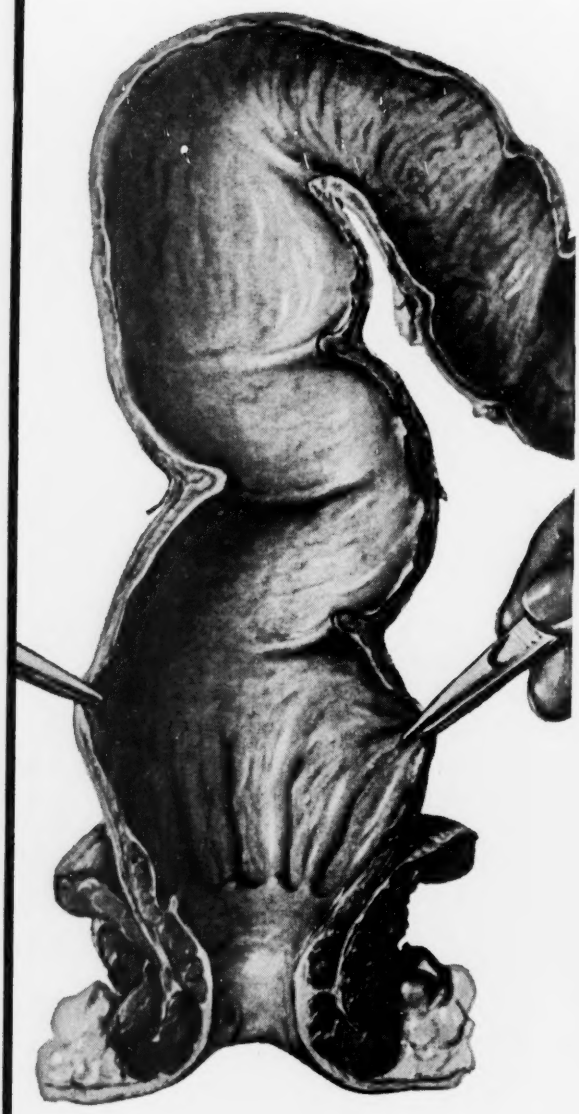

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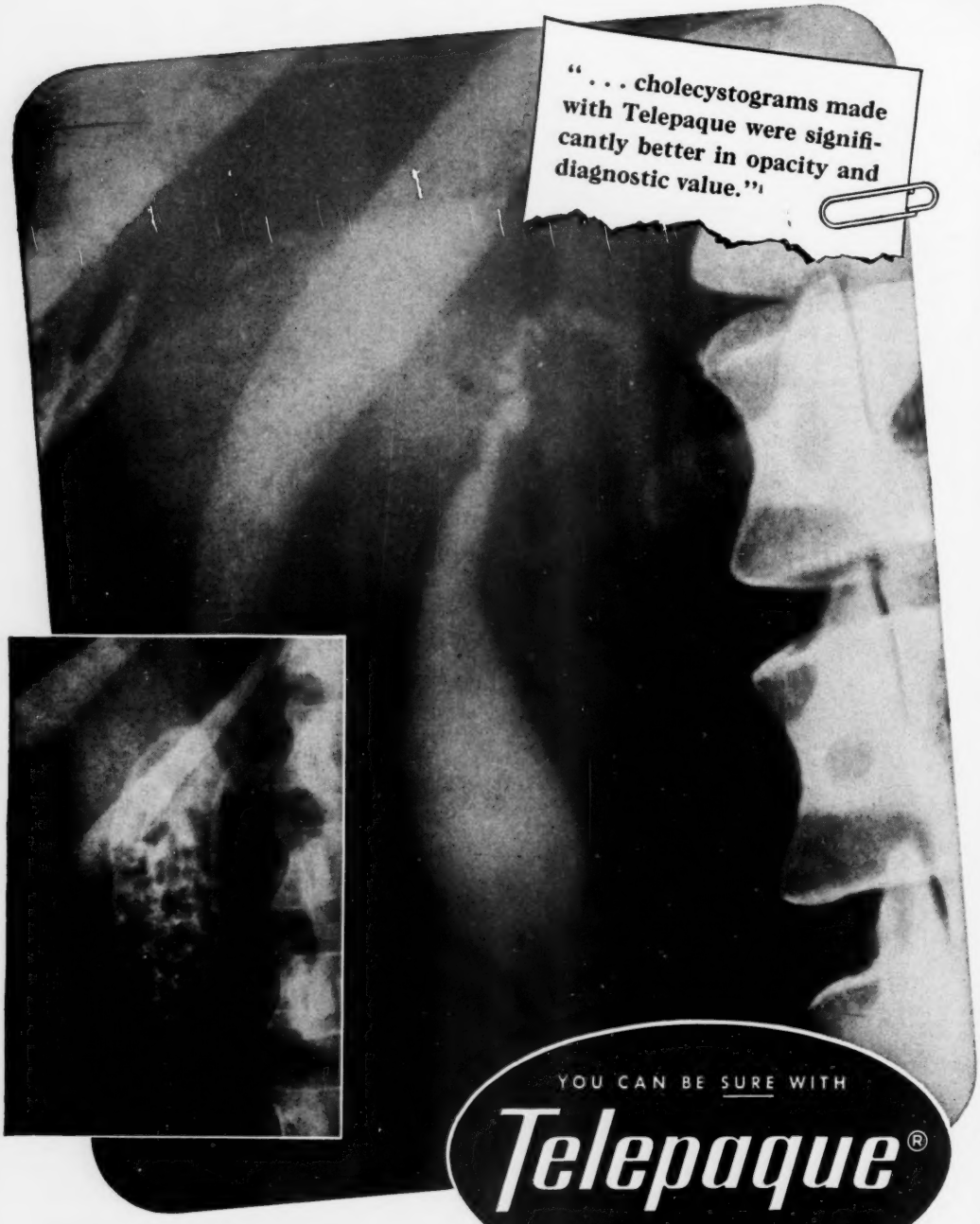

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1 Abel, M.S., Lomhoff, I.I., and Garcia, C.V.: *Permanente Found. Med. Bull.*, 10:95, Aug., 1952.
2 Lowman, R.M., and Stanley, H.W.: *Connecticut Med. Jour.*, 16:591, Aug., 1952

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1. Rev. Gastroenterology 20:744 (Oct.) 1953; abstract in J. A. M. A., 153:1580 (Dec. 26) 1953.

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Bargen, J. A.: Med. Clin. North America, 33:935 (July) 1949.

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Personal communication (Apr. 12)

1951 After-control data 1949 from 119 patients treated with Azulfidine prior to 1944 showed 90 patients (84%) symptom-free or considerably improved.

Svartz, N.: Acta Med. Scandinav. 141:172, 1951.

1952 In a series of 52 patients with chronic ulcerative colitis 30 or 58% showed significant improvement after treatment with Azulfidine.

Morrison, L. M.: Gastroenterology 21:133, 1952.

1953 Morrison publishes results from a series of 47 patients treated with Azulfidine compared to a control series of 60 patients receiving other current therapy: In the Azulfidine-series 18% are symptom-free and 52% improved, compared to 5% and 32% respectively, in the control series.

J. A. M. A.: 151:366 (Jan. 31) 1953.

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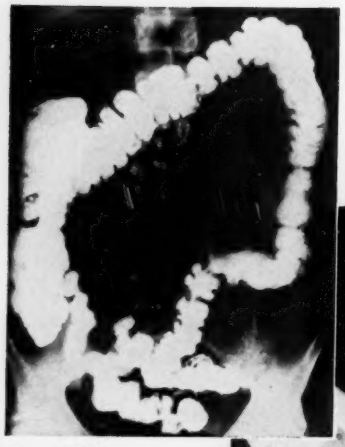

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SOME STUDIES OF NATURE AND CLINICAL SIGNIFICANCE OF PORPHOBILINOGEN

C. J. WATSON, M.D.

With the Technical Assistance of Violet Hawkinson, B.S., and Irene Bossenmaier, B.S.

MINNEAPOLIS

IT HAS been known for many years that the urine Ehrlich reaction is strongly positive in cases of acute porphyria. This was generally interpreted as due to excessive urobilinogen until 1931, when Paula Sachs [1] clearly distinguished this substance from the Ehrlich-reacting chromogen in porphyria urines. She based the distinction on differences in solubility and the failure of the porphyria chromogen upon oxidation to exhibit green fluorescence with zinc acetate. Rather, it was oxidized to a brown pigment differing from urobilin and believed to represent what the older literature had rather vaguely designated as "urofuscin." Waldenström [2] spoke of this as the "red pigment," and still later Waldenström and Vahlquist [3] studied the chromogen in more detail, confirming the observation that, unlike urobilinogen, it is not extracted from urine by most organic solvents. They noted that the Ehrlich aldehyde compound, in addition to the strong absorption band at 550 to 570 mμ, which is indistinguishable from that of urobilinogen aldehyde, exhibits a much weaker band, at 515 to 530 mμ. They observed that on heating the acidified urine there was an increase both in porphyrin and of the red-brown pigment. They regarded the chromogen as the mother substance both of porphyrin and of the brown pigment; hence, it was designated as porphobilinogen, and the brown oxidation product was named porphobilin.

ISOLATION OF CRYSTALLINE PORPHOBILINOGEN BY WESTALL'S METHOD; CONVERSION OF PORPHOBILINOGEN TO PORPHYRIN

Somewhat over a year ago it was reported from this laboratory [4] that concentrated solutions of porphobilinogen had been obtained which failed to develop porphyrin on heating at pH 4.0. At the same time another chromogen was regularly encountered which was easily converted to porphyrin by near ultraviolet irradiation.* By such conversion and removal of the porphyrin on $CaHPO_4$, solutions of porphobilinogen were obtained on many occasions which failed to yield porphyrin on heating at pH ranges of 2 to 10.0. These observations led us to believe that

From the Department of Medicine, University of Minnesota Medical School and Hospital.

Presented in part before the Association of American Physicians, Atlantic City, N. J., May 5, 1953.

Supported in part by the John and Mary Briggs Fund for research on Porphyria and under contracts with the Atomic Energy Commission and the Surgeon General's Office, United States Army, under sponsorship of the Commission on Liver Disease, Armed Forces Epidemiological Board.

* References 5 and 6.

porphobilinogen itself is not converted to porphyrin, a concept, however, which we have now abandoned, on the following grounds. Until recently, porphobilinogen had consistently defied all efforts at crystallization. Westall has lately achieved this difficult goal by virtue of a complicated procedure involving precipitation on mercury, liberation by H_2S, adsorption on an ion-exchange resin and subsequently on alumina, and crystallization from dilute acetic acid. For details reference should be made to Westall's paper.[7] We have confirmed this work and have taken cognizance of certain difficulties, which may be noted briefly.

1. Great care is essential in the preparation of the Dowex resin (200 to 400 mesh). This is made up in a slurry with N HCl and run into the column. After settling, the resin is washed with water, then regenerated by applying 2 N NaOH followed by distilled H_2O until the pH of the effluent falls to 8.0 or below. As a rule it is unnecessary to use more than a single long column (25 by 3 cm.). If porphobilin reaches the bottom before all of the solution is put on, a second column may be used. After application of a small amount of water, the porphobilinogen is eluted by ammonium acetate solution, as in Westall's method.

2. The porphobilinogen may not "hold" on the first aluminum oxide column, but in this event it has been our experience that it will nearly always hold on a second, smaller column, only those fractions being applied which exhibit a strong Ehrlich reaction.

3. It is important to elute the porphobilinogen separately from yellow or brown porphobilins also held on the alumina. Not infrequently, with Merck (Brockman) alumina, the most concentrated fractions contain porphobilin, which tends to inhibit crystallization. If these are taken onto alumina again after acidification with acetic acid to pH 4.0, it is usually possible to elute the porphobilinogen in 0.1 M NH_4OH before the porphobilin comes off.

4. A small volume of final solution is essential if crystallization is to occur. Since this is difficult to achieve if all the porphobilinogen is to be collected, we have found it advantageous to lyophilize the final ammoniacal solution. The residue is crystalline, and the material is easily redissolved in a small amount of dilute NH_4OH and recrystallized on acidification. This also permits the crystallization of very small quantities. Thus in one instance 5 mg. was obtained from a solution containing but 8 Vahlquist units (see below). Recently 487 mg. (dry weight) was obtained from a final solution containing 478 units.

We have readily confirmed the observation that crystalline porphobilinogen is converted to porphyrin, either on heating the crystals or their acid solution. This, of course, has induced us to reexamine the aforementioned porphobilinogen solutions which failed to yield porphyrin on heating, in an attempt to explain this apparent discrepancy. The possibility existed that certain conditions such as pH, buffer capacity, or ionic strength were responsible for our previous observations. Herbert [8] and, more recently, Brockman and Gray [9] have emphasized the significance of the latter factors. Westall [7] observed porphyrin formation from crystalline porphobilinogen in solutions of widely varying buffer concentration and ionic strength, and, while recognizing the inhibiting effect of buffer salts, he noted more conversion with greater ionic strength, the optimum being at 0.5 N HCl, although considerable formation occurred at pH 4.0 (acetic acid-sodium acetate buffer).

Certain evidence has been obtained in the present study suggesting that porphobilinogen exists in two forms, A and B, and that the A form, on heating, is converted only to porphobilin. In a series of experiments, solutions of the type previously described,[4] failing to yield porphyrin on heating, were subjected to Westall's Hg precipitation and H_2S regeneration. The resulting porphobilinogen solution exhibited plentiful porphyrin formation when heated (Table 1). When this B solution was mixed in equal parts with Solution A (not treated with mercury) and

heated, the amount of porphyrin formed was that anticipated from the B solution alone, suggesting that some essential difference existed in the state of the porphobilinogens in the two solutions. Since in these experiments, however, the pH was not determined, further studies were carried out in which Type A and B solutions

TABLE 1.—*Porphyrin Formation on Heating Porphobilinogen Solutions (A and B) and Mixtures*

Exper. No.	Porphobilinogen Solution A, Cc.	Porphobilinogen Solution B, Cc.	H_2O, Cc.	Uroporphyrin After Heat,* γ: By Direct Fluorimetry	Uroporphyrin After Heat,* γ: After $CaPHO_4$ Precipitation
1. (*a*)	6	..	6	...	0
(*b*)	..	6	6	186	180
(*c*)	6	6	..	196	186
2. (*a*)	10	..	..	0	...
(*b*)	10	..	10†	0	...
(*c*)	..	10	10†	280	...
(*d*)	..	10	..	284	...
3. (*a*)	10	..	10	0	...
(*b*)	..	10	10	21.2	...
(*c*)	10	10	..	22.4	...

* Twenty minutes at 80 C. Prior to heating HCl was added to each solution in an amount calculated to make 0.1 N, not taking into account any buffer activity. The pH was not determined. The reaction was acid in each instance.

† Instead of water, a control solution prepared from normal urine was employed. This was prepared in the same manner as the Type B porphobilinogen solution, after which it was treated with mercuric acetate, as in Westall's method. Since no precipitate occurred, a small amount of Na_2CO_3 was added; the resulting precipitate was filtered, suspended in water, and the Hg was precipitated with H_2S. The clear filtrate, after aeration, was used in the above.

TABLE 2.—*Effect of Mercuric Acetate Precipitation on Porphyrin Formation in Crude Porphobilinogen Solutions* Before and After Treatment with Mercuric Acetate*

Tube	Solution A, Cc.*	Solution B, Cc.*	1% Acetic Acid, Cc.	1.5 N HCl, Cc.	H_2O, Cc.	pH	Fluorescence	γ Uroporphyrin After Δ 80 C. 30 Min.†
1	1.0	...	0.25	...	...	3.0	Blue	0
2	1.0	...	....	0.1	...	2.2	Blue	0
3	1.0	...	....	0.2	...	1.4	Blue	0
4	1.0	...	....	0.35	...	0.86	Blue	0
5	1.0	...	....	0.5	...	0.73	Red	3.2
6	1.0	...	....	1.0	...	0.4	Red	3.15
7	1.0	...	....	...	1.0	3.8	Blue	0
8	...	1.0	0.25	...	...	3.5	Red	4.68
9	...	1.0	....	0.1	...	2.45	Red	4.4
10	...	1.0	....	0.2	...	1.82	Red	3.95
11	...	1.0	....	0.5	...	0.78	Red	3.58
12	1.0	1.0	0.25	...	...	3.25	Gray	2.8
13	1.0	1.0	....	0.5	...	0.65	Red	6.92

* Solution A, porphobilinogen solution as previously described,[4] 1.9 units per cubic centimeter. Solution B, the same after treatment with mercuric acetate, H_2S, and aeration, as in Westall's method.

† Direct fluorimetry after dilution to 10 cc. with 1.5 N HCl.

and mixtures were heated at various pH ranges, as seen in Tables 2 and 3. It is seen in Table 2 that with the A solution there was no porphyrin formation until the pH was nearly 0.7, and a striking difference is observed as the acidity increases from 0.86 to 0.73. On the contrary, after mercury treatment a marked porphyrin formation is seen at pH 3.5. Similar data are shown in Table 3, in which Solution

B, however, was one of crystalline porphobilinogen. Again a critical difference is noted as the acidity increases from pH 0.88 to 0.75. In Tables 2 and 3 there is some evidence of inhibition of porphyrin formation from the B porphobilinogen by the equal amount of A solution; in the main, however, the data appear to indicate a difference in state of the porphobilinogen, and it appears doubtful that the differences can be explained as due to variations in ionic strength and/or buffer capacity. Indeed, the result is difficult to explain except on the basis of the existence of two forms of porphobilinogen, but whether this difference is molecular or due to a complex with some constituent of the urine is unknown. Schwartz and associates [10] have found evidence of at least two forms of porphobilinogen on the basis of certain elution characteristics and the solubility of the respective aldehyde compounds in butyl alcohol. This is to be described in more detail separately. These findings are not, however, necessarily related to the differences in Tables 1, 2, and 3.

TABLE 3.—*Effect of pH on Conversion of Porphobilinogen to Porphyrin, Comparing the Crude 1% Acetic Acid Eluates as Previously Described (Solution A) with Crystalline Porphobilinogen (Solution B).*

Tube	Solution A	Solution B *	10% Acetic Acid, Cc.	1.5 N HCl, Cc.	Distilled H_2O, Cc.	pH	Fluorescence in UV Light	Uroporphyrin in Sample After 80 C. 30 Min., γ †
1.	1.0	...	....	...	...	3.89	Blue	0
2.	1.0	...	....	...	2.0	3.9	Blue	0
3.	1.0	...	0.25	...	0.75	3.05	Blue	0
4.	1.0	...	....	0.1	0.9	2.3	Blue	0
5.	1.0	...	....	0.2	0.8	1.5	Blue	0
6.	1.0	...	....	0.35	0.65	0.88	Blue	0.02
7.	1.0	...	....	0.5	0.5	0.75	Red	1.8
8.	...	...	....	...	2.0	3.87	Blue	0.7
9.	...	1.0	0.25	0.2	1.8	1.6	Red	1.94
10.	1.0	1.0	0.35	...	1.0	3.8	Blue	0.69
11.	1.0	1.0	0.25	1.0	...	0.95	Red	4.4
12.	1.0	1.0	0.25	0.5	0.5	1.2	Red	2.85
13.	1.0	1.0	0.25	0.2	0.8	2.3	Blue	0.42

* 0.23 mg. crystalline porphobilinogen in 10 cc. 0.1 M NH_4OH.
† Direct fluorimetry after dilution to 10 cc. with 1.5 N HCl.

Certain spectroscopic characteristics of porphobilinogen suggest the possibility of differing molecular character under some circumstances. Thus, Waldenström and Vahlquist [3] noted that if an alkaline solution of porphobilinogen is briefly heated the aldehyde compound no longer exhibits the β absorption band at 515 to 530 mμ. We have observed an aberrant spectrum of the Ehrlich aldehyde compound formed with certain weakly ammoniacal solutions of porphobilinogen which have stood at room temperature for several days. In these, two equally intense bands were noted, α at 588 and β at 552 mμ (maximum). A shift to this form is also noted when the solution of the aldehyde compound of crystalline porphobilinogen is allowed to stand several hours or overnight at room temperature. The basis of these variations is unknown and requires further study.

Some study has been made of the possibility that the failure of the above-mentioned A solutions to yield porphyrin on heating is due to formation of a complex with some constituent of the urine during preparation of the crude Type A solution.[4] It is possible that a loose complex exists in the native acute porphyria urine, but,

if so, it appears that it interferes but relatively little with porphyrin formation, as this usually proceeds well on heating the urine adjusted to pH 4.0 with acetic acid. It is possible that special conditions prevail in porphyria urine to permit release of porphobilinogen from such a complex on heating; quantitative relationships may be

TABLE 4.—*Effect of Fresh Normal Urine on Conversion of Porphobilinogen to Porphyrin by Heat**

0.1 M NH_4OH Solution Crystalline Porphobilinogen Containing Approx. 0.4 Mg./Cc.	Porphyrin, γ/Cc.	pH
(*a*) 1 cc. + 4 cc. urine + 0.2 cc. 3 N HCl	5.3	1.68
(*b*) 1 cc. + 4 cc. urine + 0.2 cc. glacial acetic acid	15.0	3.62
(*c*) 1 cc. + 4 cc. urine + 0.2 cc. 10% NaOH	2.7	9.60
(*d*) 1 cc. + 4 cc. H_2O + 0.2 cc. 3 N HCl	105.6	1.02
(*e*) 1 cc. + 4 cc. H_2O + 0.2 cc. glacial acetic acid	42.9	3.05
(*f*) 1 cc. + 4 cc. H_2O + 0.2 cc. 10% NaOH	17.0	12.1
(*g*) 4 cc. urine + 1 cc. H_2O + 0.2 cc. 3 N HCl	0.09	1.67

* 80 C. for 30 minutes.

TABLE 5.—*Failure of Zn Complexing to Block Porphyrin Formation on Heating a Solution of Crystalline Porphobilinogen**

1. 1 cc. porphobilinogen solution + 0.05 cc. alcoholic Zn acetate solution. After several minutes mixed with 0.25 cc. 10% glacial acetic acid and 0.7 cc. distilled H_2O pH 4.0.
2. 1 cc. porphobilinogen solution + 0.05 cc. 95% alcohol + 0.25 cc. 10% glacial acetic acid + 0.7 cc. distilled H_2O.

Both 1 and 2 subjected to 80 C. for 30 minutes.

1. Faint orange yellow fluorescence in ultraviolet light (definite metal complex fluorescence spectrum).
2. Strong red fluorescence in ultraviolet light.

1 cc. 1.5 N HCl added to 1 and 2.

Both now show equally intense red fluorescence.

1. 3.78 γ uroporphyrin.
2. 4.25 γ uroporphyrin.

This difference was believed insignificant.

* 0.23 mg. crystalline porphobilinogen per 10 cc. 0.1 M NH_4 OH.

TABLE 6.—*Inhibition of Porphyrin Formation from Porphobilinogen by Uric Acid*

0.1 M NH_4 OH Solution Crystalline Porphobilinogen 0.5 Units/Cc.	Uroporphyrin, γ
1. 2 cc. porphobilinogen solution + 2 cc. uric acid solution *	94
2. 2 cc. porphobilinogen solution + 2 cc. urea solution *	360
3. 2 cc. porphobilinogen solution + 2 cc. creatinine solution *	439
4. 2 cc. porphobilinogen solution + 2 cc. NaCl solution *	326
5. 2 cc. porphobilinogen solution + 2 cc. 0.5% KOH solution *	403

* 1 cc. glacial acetic acid was added to each and the solutions were heated at 80 C. for 30 minutes. Uric acid, creatinine, urea, and NaCl solutions, 5 mg. per cubic centimeter, in 0.5% KOH.

important in this respect. Nevertheless, as noted in the following, some urine samples are encountered in which heating at pH 4.0 fails to bring about porphyrin formation, and in others the formation is slight. Normal urine markedly depresses porphyrin formation from crystalline porphobilinogen dissolved in dilute ammonia and added to it, the mixture being then acidified and heated. Typical data are shown in Table 4. Zinc, which is complexed with the Waldenström porphyrin in acute

porphyria urine, may also complex with porphobilinogen, but, at least under the conditions employed, in vitro, it has not interfered with porphyrin formation in heated solutions of crystalline porphobilinogen (Table 5). Uric acid, urea, creatinine, and sodium chloride have also been studied, and of these only uric acid has been found to depress porphyrin formation (Table 6). It is seen that porphyrin formation was not entirely prevented, but it is recognized that the experimental conditions may not have been optimal, as compared with those under which uric acid might complex with porphobilinogen in the urine or in the body. It is perhaps significant that the A solutions have been found to contain considerable uric acid and also that Brockman and Gray [9] noted uric acid in their crude porphobilinogen solutions. Cookson and Rimington [11] and Granick and Bogorad [12] have now shown that porphobilinogen is a monopyrrole rather than a dipyrrylmethene, as first postulated by Waldenström and Vahlquist.[2] They have presented strong evidence for a formula which is in accord with the recent work of Shemin and associates † on the essential nature of glycine and a succinyl intermediate in the tricarboxylic acid cycle in porphyrin biosynthesis. The formula proposed for porphobilinogen [11] is in accord with the possibility of a complex with uric acid.

The uroporphyrin obtained on heating crystalline porphobilinogen has not yet been identified with certainty. Cookson and Rimington [11] report that it is mainly uroporphyrin III but also contains some other unidentified isomer in minor proportions. We have now isolated and decarboxylated it repeatedly, to study the coproporphyrin thus derived. This study is continuing and will be reported in detail elsewhere. Suffice it to say now that the uroporphyrin, and the coproporphyrin mixture obtained from it, are dissimilar in many respects from the Waldenström porphyrin which we have isolated from acute porphyria urine. Recent studies by Falk, Dresel, and Rimington [15] with red cell hemolysate and by Bogorad and Granick [16] with a Chlorella mutant have shown that these systems convert crystalline porphobilinogen to a number of porphyrins, including uroporphyrin, coproporphyrin, and protoporphyrin. Falk and Rimington have not identified the isomer type of the uroporphyrin formed in their experiments but assume that it is III, as their data suggested that it was a precursor of the protoporphyrin which was also formed.‡ Granick, however, finds that uroprophyrin I and III are both elaborated from the porphobilinogen by the Chlorella mutant. In the first few hours uroporphyrin III was noted, later to be replaced entirely by the Type I isomer. The supernate was also found capable of this conversion, but if it was first heated at 55 C. only uroporphyrin I was formed. This indicates that the enzyme necessary for conversion to the Type III series is relatively heat-labile. The primary appearance and subsequent disappearance of uroporphyrin III in the cultures of this mutant with later appearance of Type I might be explained as a further conversion § of Type

† References 13 and 14.

‡ In a recent study, to be reported elsewhere, Schwartz has been unable to show conversion of uroporphyrin to coproporphyrin or protoporphyrin, or of coproporphyrin to protoporphyrin, whether by red cell hemolysate or liver homogenate. With each, however, the conversion of crystalline porphobilinogen to uroporphyrin, coproporphyrin, protoporphyrin, and other unidentified porphyrins was easily demonstrated. The study with living systems is being extended at the present time.

§ See the preceding footnote.

III, but not of Type I, to protoporphyrin.[16] From these studies it is at least evident that porphyrin formation from porphobilinogen in vivo may differ significantly from that on heating in vitro.

It has been noted previously || that porphobilinogen is often accompanied in acute porphyria urine by an Ehrlich-negative chromogen convertible to porphyrin by near ultraviolet radiation for several minutes. This has been confirmed by Herbert,[8] but Brockman and Gray [9] have failed to observe it in urine samples of four cases. In our earlier papers ¶ it was stated that this chromogen was extractable from urine by ethyl acetate at pH 4.0, but we have found more recently that extraction at gray-blue Congo reaction (pH 3.2) is considerably more efficient, just as Waldenström and co-workers [17] found for the uroporphyrin complex in these urines. The porphyrin derived from this precursor has been isolated repeatedly and is receiving further study, to be described elsewhere. It should be noted that no porphyrin formation is observed on similar radiation of porphobilinogen in acid or alkaline solution, although the Ehrlich-negative chromogen is readily converted to porphyrin in 1% acetic acid as well as in ethyl acetate. Its behavior is somewhat reminiscent of that of the uroporphyrinogen obtained by amalgam reduction of uroporphyrin I, but there is reason to believe that they may not be identical. The conversion to uroporphyrin of the Ehrlich-negative precursor, extracted from acute porphyria urine by ethyl acetate, by shaking with a dilute iodine solution and subsequent extraction with 3% sodium acetate solution, as previously described,[5] has also been confirmed repeatedly.

PORPHOBILINOGENURIA

Regardless of the fundamental nature of porphobilinogen and its relation to porphyrin formation, its demonstration in the urine is clearly of the utmost value in the diagnosis of acute porphyria. It was reported from this laboratory a number of years ago [18] that, in addition to the general insolubility of the substance itself in organic solvents, its Ehrlich aldehyde compound is insoluble in chloroform, in contradistinction to that of urobilinogen, which is readily extracted. In cases of acute porphyria this simple test is consistently positive during the attack, and hence it constitutes the most useful screening test for this disease. In 89 cases of the intermittent acute type, all have shown positive reactions at least during the period of relapse and many, in lesser degree, during remission as well. Hammond and Welcker [19] sought to answer the question as to whether a positive test is strictly pathognomonic of porphyria. They examined 1,000 urine samples from as many persons, representing a general hospital population. No positive tests were encountered. This at least indicates the relative infrequency of false-positive reactions. Nevertheless, it is clear that significantly positive tests are encountered in association with other, serious disease, in the absence of any ordinary manifestations of porphyria. In the course of thousands of tests during the past 15 years we have recorded significantly positive results in 11 cases which could not well be classified as porphyria. These fell into three categories: (1) neoplastic disease, (2) severe liver disease, and (3) nervous system disease (Table 7). The positive tests in these cases are exceptional, as many other cases of the same general type have negative

|| References 4-6.

¶ References 5 and 6.

reactions. This raises the question as to whether these persons had a latent porphyria trait, which is undoubtedly more common than has been supposed. On the other hand, it is entirely possible that if a suitable method of detecting small amounts, by concentration, had been available many more instances of porphobilinogenuria would have been encountered. We have recently been using a method of concentration depending upon calcium acetate-acetone precipitation# and with this have uncovered several cases, including one of lead poisoning, in which the ordinary test was negative but in which small amounts of porphobilinogen were nevertheless demonstrable. This would appear to make a constitutional factor less essential, and, indeed, the fact that rabbits, rats, and mice with allylisopropylacetylcarbamide (Sedormid) poisoning [20] regularly excrete large amounts of porphobilinogen would seem to

TABLE 7.—*Urinary Porphobilinogen and Porphyrins in Diseases Other than Definite Porphyria*

Case	Sex	Age, Yr.	Clinical Features	Porphobilinogen	Urine Uroporphyrin γ/Day *	Coproporphyrin γ/Day	Type III Coproporphyrin, %
1. Liver disease							
A. J.	M	30	Ch. Brucellosis, jaundice, ascites, death in hepatic coma; adv. cirrhosis	++++	40	220-648	57-86
J. M.	F	50	Recovering from subacute atrophy	+	0	300	.....
L. L.	M	49	Cirrhosis	+	45	196-551	40-52
2. Malignant disease							
W. B.	M	34	Hodgkin's disease, HN_2 therapy; died	+	98	350-1,300	80
L. H.	F	53	Reticuloendotheliosis; sporotrichosis	++++	300-1,280	520-1,640	82
F. W.	F	55	Lymphoblastoma (biopsy)	++	Trace	1,600-16,870	99
M. K.	F	55	Metastatic carcinomatosis	++	162-280	328-1,370	.....
3. Infectious and nervous disease							
K. P.	M	23	Bulbar poliomyelitis	+	90	1,000	62
J. F.	M	61	Tetanus under flaxedil therapy	++	0-27	244-857	75
L. M.	M	41	Guillain-Barré syndrome	+	Trace	361	.....
B. B.	M	23	Rheumatic fever; subacute bacterial endocarditis; nausea, vomiting	++	0	392	70

* The values given here and in Table 8 relate to the use of only 5 cc. of urine; hence in some instances, because of low concentrations, the galvanometer readings were insignificant and the values are recorded as 0, although it is probable that traces were present, since they are regularly demonstrable in normal urine if larger volumes are employed.

indicate an acquired abnormality. Here, at least, the phenomenon is clearly a general characteristic of the species rather than a peculiar reaction of exceptional individuals. One must still entertain the probability that only an occasional human being, because of inborn metabolic differences, reacts to a given stimulus by excreting porphobilinogen. Despite the occasional "false" positive test, whatever its underlying significance, the ordinary Ehrlich aldehyde reaction with $CHCl_3$ insolubility is generally clear-cut in its practical meaning, especially when considered in relation to the clinical manifestations. From a diagnostic standpoint it is fortunate that in acute porphyria porphobilinogen is present in large amounts, with little or no urobilinogen, so that the contrast between aqueous and chloroform phases is outspoken. On occasion, in other conditions, faint pink or orange reactions, chloroform-insoluble, may be

With S. Schwartz, to be published.

somewhat perplexing and are of unknown origin. It has been our policy to disregard any reaction of this type unless a definite α absorption band can be made out with a hand spectroscope, maximum at 560 to 565 mμ.* The additional presence of a weaker β absorption, 515 to 530 mμ, is even more convincing. A further helpful point is that most of the porphobilinogen aldehyde color develops at once † when an equal volume of Ehrlich's reagent is added to the urine, while the urobilinogen aldehyde color only develops in any considerable extent after diluting with water, alcohol, or, preferably, a saturated sodium acetate solution, as is used in quantitative urobilinogen determinations.[21] Certain urines rich in urobilinogen may exhibit a small fraction of aldehyde color not extractible by chloroform. In such instances two further simple aids in differentiation are available: (1) a 1:5 dilution of the urine prior to carrying out the reaction and (2) extraction of the urine, after acidification with acetic acid, with several volumes of ethyl acetate.‡ This removes urobilinogen quantitatively but removes relatively little porphobilinogen. If the aqueous solution now persists in exhibiting an Ehrlich reaction after three extractions with ethyl acetate and if the aldehyde compound is insoluble in chloroform, it is safe to conclude that porpho-

TABLE 8.—*Isolated Porphobilinogenuria; Probable Porphyria*

Case	Sex	Age, Yr.	Clinical Features	Urine Porphobilinogen	Urine Uroporphyrin	Urine Coproporphyrin/Day	Type III, %
C. C.	M	49	Ch. diarrhea 20 years; abdominal pain, nausea, vomiting; B. P. 160/100	+	0	100-240	80
M. P.	F	72	Ch. neurosis; arthralgia; vomiting; B. P. 200/82	+	0	250-500	82
H. F.	F	43	Psychosis; pain in arm and shoulder; disturbed, uncooperative	+	0	258-380	74
B. O.	F	29	Many attacks of abdominal colic; 10 laparotomies without diagnosis	++-0	0*	100-253	90

* In this instance no uroporphyrin was demonstrable after heating the porphobilinogen-containing urine at 80 C. for 30 minutes (pH 4.0).

bilinogen is present. Our observations indicate that small amounts of porphobilinogen at times accompany large excesses of urobilinogen, especially in cases of liver disease. Further study of this problem is in progress.

* Vahlquist [22] and Westall [7] indicate a maximum at 552 mμ, but, as seen in Chart 1, peak absorption in the Beckman DU spectrophotometer is at 556 mμ. Mid absorption as measured in a carefully calibrated Zeiss grating spectrometer (Löwe-Schumm type) is at 562 mμ, the edge of the band being at 552. (The sensitivity of this spectrometer is $\pm$ 5Å.) The β absorption band in the same solutions served as a control, since its maximum, at 522 mμ, was identical with the two methods. Also, the absorption band of urobilinogen aldehyde, although undistinguishable from the α band of porphobilinogen aldehyde in the Zeiss spectrometer (maximum 562 mμ), is significantly stronger at 562 than at 556 mμ in the Beckman spectophometer. The nature of this apparent discrepancy has not been determined.

† Under certain circumstances differing porphobilinogen(s) are excreted, either alone or in association with the Westall type. Distinction is based upon a number of differing physical characteristics, which will be described in detail in a separate communication by Schwartz and associates. Among these differences are ethyl acetate solubility and a much greater development of Ehrlich aldehyde color intensity after addition of sodium acetate solution. Unlike urobilinogen, however, this differing porphobilinogen is not extracted by petroleum ether, and its aldehyde compound is not extracted by $CHCl_3$.

‡ See previous footnote.

Brief reference must be made to cases of porphyria exhibiting definite porphobilinogenuria without any increase of uroporphyrin. Waldenström also observed such instances.[2] Some of these cases have shown distinct increases of coproporphyrin, mainly of the Type III isomer (Table 8). In certain cases the attack and the associated porphobilinogenuria may be remarkably brief, and during the remission the urine examination may fail entirely in establishing the diagnosis. In cases of unexplained abdominal pain, acute or subacute neuropathy, or nervous system

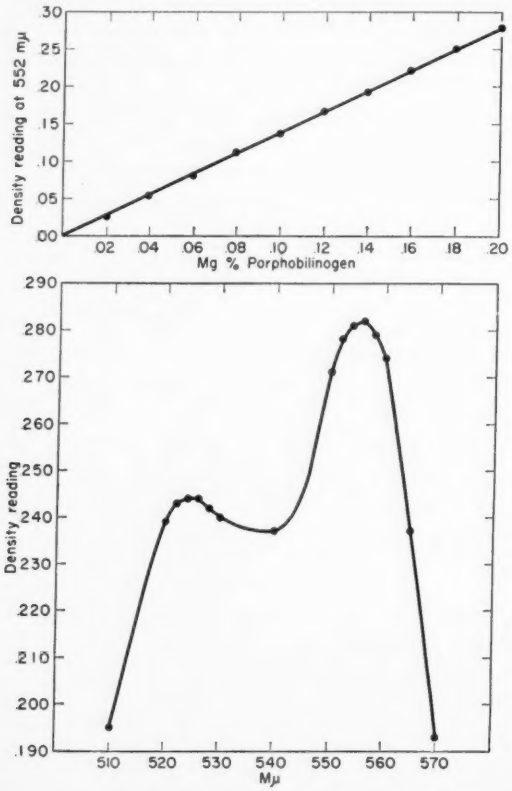

Chart 1.—Upper plot, optical density of porphobilinogen aldehyde solution as determined in the Beckman Spectrophotometer at 552 mμ. Equal parts of a 0.1 M NH_4OH solution of crystalline porphobilinogen and Vahlquist-type Ehrlich reagent were mixed and the reading taken. The values along the abscissa represent the final porphobilinogen concentration. Lower plot, spectral distribution curve of porphobilinogen aldehyde solution prepared as above with crystalline porphobilinogen.

affection it is therefore advisable to examine the urine at the height of the attack, if at all possible.

While it is clear that heating an acidified porphobilinogen-containing urine results in a marked increase of uroporphyrin-type porphyrins, it seems reasonable, at least in the light of present knowledge, to determine the porphobilinogen and preformed porphyrins in alkalinized relatively fresh urine samples, without heating.

Porphobilinogen is relatively stable in alkaline solution. Heating the acidified urine prior to determining the porphyrin content has several disadvantages: 1. While the uroporphyrin increases to a variable and usually marked extent, it is clear that the conversion of porphobilinogen to porphyrin is not quantitative and varies considerably under different conditions; furthermore, as mentioned in the foregoing, there is reason to believe that the type of porphyrin formation may differ from that occurring in vivo. 2. Porphobilinogen is undoubtedly of great significance from a physiological standpoint and should be determined individually if at all possible. If this is done, the most important information will be gained, and to heat the urine and determine the uroporphyrin will only provide inaccurate and artifactual values. 3. Heating causes significant diminution of coproporphyrins, thus requiring a separate determination.

TABLE 9.—*Variability in Porphobilinogen Aldehyde Color Intensity with Changes in the Solution*

	Solution, Cc.	Ehrlich's Solution, Cc.	NaOAc Solution, Cc.*	H_2O, Cc.	Color Units/ Mg.
A. 0.52 mg. crystalline porphobilinogen in 10 cc. 0.1 M NH_4OH					
1	0.2	0.2	0.4	9.2	0.40
2	0.2	0.4	0.8	8.6	0.57
3	0.2	0.6	1.2	8.0	0.62
4	0.2	0.6	0	9.2	0.46
B. 1 cc. solution A + 9 cc. normal (Ehrlich-neg.) urine					
1	2.5	2.5	5.0	...	0.70
2	2.5	7.5	15.0	...	1.21
C. 1 cc. solution A + 9 cc. H_2O					
1	2.5	7.5	15.0	...	1.92
2	5.0	5.0†	0	...	2.11
D. 0.5 mg. crystalline porphobilinogen in 50 cc. 0.1 M NH_4OH					
1	5.0	5.0†	90.0	...	0.64
E. 1 cc. solution D + 9 cc. H_2O					
1	5.0	5.0†	0	...	0.48
2	5.0	5.0	0	...	0.36

* Saturated sodium acetate solution.
† In these runs the Vahlquist-type Ehrlich reagent was used (20 gm. *p*-dimethylaminobenzaldehyde in 500 cc. concentrated HCl + 500 cc. H_2); in all others the reagent used was made in the proportion of 0.7 gm. of the aldehyde, 150 cc. concentrated HCl, 100 cc. H_2O.

Nevertheless, the quantitative determination of porphobilinogen in the urine offers genuine difficulty. Westall [7] stated that 1 mg. of crystalline porphobilinogen was equivalent to 130 Vahlquist units.[22] The latter is defined as the Ehrlich aldehyde color intensity of 1 mg. of urobilinogen per 100 cc. Actually, Vahlquist [22] used the extinction coefficient which Heilmeyer [23] had previously obtained with a spectrophotometer, applying this arbitrarily to the stufenphotometer. Westall's value would indicate that crystalline porphobilinogen gives an aldehyde color 130 times stronger than that of urobilinogen. This is evidently based, however, on 1 mg. per cubic centimeter of urobilinogen rather than on 1 mg. per 100 cc., as stated by Vahlquist. Westall,§ using the Beckman spectrophotometer at 552 mμ, noted a galvanometer reading of 0.545 with a concentration of 0.38 mg. per 100 cc. In the present study the optical density of the aldehyde compound of recrystallized porphobilinogen, first dried to constant weight in vacuo, at room temperature, is in good agreement with

§ Personal communication to the author.

this value, as noted in the upper plot in Chart 1, assuming that Beer's law is obeyed on extrapolation to the 0.38 mg. level. In other runs, with concentrations ranging up to 1.00 mg. per 100 cc., this has been found true.

Under various conditions, as mentioned below, it was found that a final concentration of 1 mg. of crystalline porphobilinogen per 100 cc. has an Ehrlich aldehyde intensity equivalent to that of 0.4 to 2.1 mg. of urobilinogen per 100 cc., or Vahlquist units. With this value the order of magnitude of porphobilinogen concentration in acute porphyria urine is from 20 to 200 units per liter, in agreement with the observations of Waldenström and Vahlquist,[24] whereas Westall [7] referred to 4,000 units per liter.

Considerable variation in color intensity is encountered, depending on various factors, as seen in Table 9. It should be noted too, that the type of Ehrlich reagent employed is very significant. The reagent which we have used for urobilinogen determination,[21] prepared in accordance with H. Fischer's method,|| is not as concentrated as that of Vahlquist [22] and produces a less intense aldehyde reaction (Table 10). With the Vahlquist or strong Ehrlich reagent the maximum color is attained within a few seconds, while with the weaker solution, such as we have used for urobilinogen, it develops more slowly, often requiring an hour or more to reach completion.

TABLE 10.—*Variations in Ehrlich Aldehyde Color Intensity With Strong and Weak Ehrlich Reagents, With and Without Additional Saturated Sodium Acetate Solution*

	Dilute Solution of Crystalline Porphobilinogen, Cc.	Weak Ehrlich Reagent, Cc.	Vahlquist-Type Ehrlich Reagent, Cc.	NaOAc Solution, Cc.*	Color Units/Cc.†
1	5	..	5	..	0.10
	5	..	5	10	0.15
	5	5	..	..	0.071
	5	5	..	10	0.098
2	5	..	5	..	0.128
	5	..	5	10	0.193
	5	5	..	..	0.072
	5	5	..	10	0.10

* Saturated aqueous sodium acetate solution.
† Evelyn 550 filter; see Chart 1.

In Chart 1 it is seen that the porphobilinogen aldehyde compound obeys Beer's law in the range of concentration noted. This is in accord with Vahlquist's observations. However, a principal obstacle to the development of a precise quantitative method for determination of urinary porphobilinogen is the variability of aldehyde color intensity with relatively slight change in conditions. Significant differences are observed with the same amount of porphobilinogen dissolved in urine rather than in water, or when dilution with water is made before rather than after the formation of the aldehyde compound (Table 9). It is doubtful that any direct application of the Ehrlich reaction to the urine will permit more than a rough approximation, but it is possible that a primary precipitation with mercury, as in Westall's method, or with calcium acetate-acetone, as mentioned previously, may provide the standard

|| Personal communication to the author.

conditions necessary for an exact quantitative procedure. This is being studied further. Pending development of a more precise technique, it is believed preferable to use the simple method of determining the urine Ehrlich reaction for urobilinogen,[21] substituting the Vahlquist type of reagent and employing two volumes of sodium acetate solution. It is convenient to use 5 cc. of urine (diluted appropriately if the initial Ehrlich reaction is strong), 5 cc. of reagent, and 10 cc. of the saturated sodium acetate solution. The solution is filtered into an Evelyn tube and read in the Evelyn colorimeter with the 550 filter. It may be noted that with this filter the

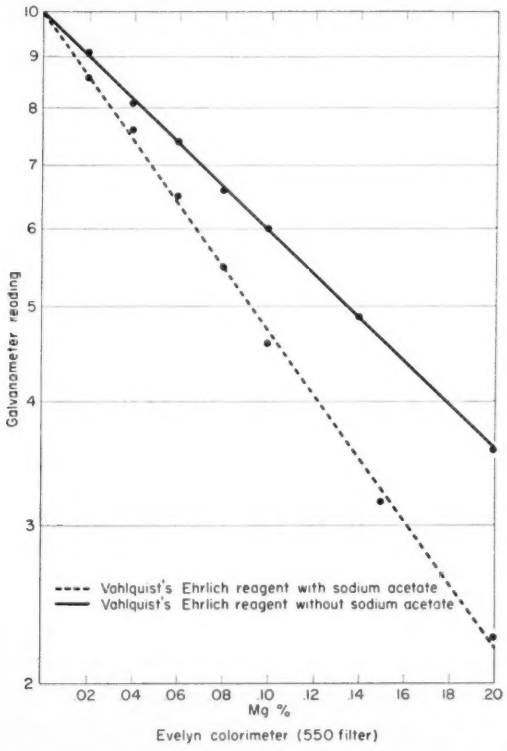

Chart 2.—Plot on semilog paper of the optical density of porphobilinogen aldehyde solution prepared as for Chart 1. Values along the abscissa represent the final concentrations of porphobilinogen. The sodium acetate was added in a saturated aqueous solution in a 1:1 ratio with the combined porphobilinogen and Vahlquist-type Ehrlich aldehyde reagent.

optical density of the porphobilinogen aldehyde is approximately 10% greater than with the 565 filter. The blank is prepared by adding the sodium acetate and Ehrlich's reagent in reverse and filtering. This should be used at once, as porphobilinogen aldehyde color develops very slowly even in acetic acid, in the presence of sodium chloride, owing to formation of small amounts of HCl. The concentration may then be obtained from the lower plot in Chart 2. As already noted, it is doubtful that this is more than an approximation, owing to variation in conditions with

different urine samples. Unless the aldehyde compound in any given instance has shown a characteristic absorption band, maximum 560 mμ, and is not extractible by chloroform, the determination of optical density should not be made.

SUMMARY AND CONCLUSIONS

Crystalline porphobilinogen has been isolated repeatedly from acute porphyria urine by Westall's method. As shown by Westall, the substance is partially converted to a uroporphyrin-type porphyrin by heating the crystals or their acid solutions. The exact nature of the uroporphyrin thus formed remains to be determined. The question of differences in the in vivo formation of porphyrin from porphobilinogen is considered.

Our previous belief that porphobilinogen is not convertible to porphyrin is incorrect. This was based on misinterpretation of two observations which in themselves have now been confirmed repeatedly, i. e., 1. There is an Ehrlich-negative porphyrin chromogen in porphyria urines. This substance is readily converted to porphyrin by iodine or exposure to ultraviolet light but not by heat. 2. Certain porphobilinogen solutions, heated at a pH range of 2 to 6, do not exhibit porphyrin formation. It has been found that, in contradistinction to pure porphobilinogen, which is quickly converted to porphyrin on heating in acid solution at a wide range of pH, the solutions previously described must be strongly acidified with HCl to a critical pH of 0.7 to 0.8 and heated before porphyrin formation occurs. Some evidence has been obtained indicating that this may be due to complexing with a normal urine constituent, possibly uric acid.

While the occurrence of porphobilinogen in the urine is very characteristic of acute porphyria, and of great significance in diagnosis, a porphobilinogen is also encountered at times in association with diseases which cannot be classified as porphyria. A group of 11 cases is described, subdivided into (1) liver disease, (2) malignant disease, and (3) infectious or nervous disease. Whether these persons had latent porphyria or whether the porphobilinogenuria was strictly secondary is not clear. Whether this porphobilinogen is identical with that of acute porphyria remains to be determined.

The occurrence of certain atypical cases best classified as porphyria, characterized by porphobilinogenuria with little or no porphyrinuria, is reemphasized.

Certain aspects of the optical behavior of porphobilinogen aldehyde are discussed, with special reference to the problem of quantitative determination.

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FATAL CORONARY HEART DISEASE

Clinicopathologic Patterns and Other Features in One Hundred Consecutive Cases

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THIS REPORT represents a clinicopathologic analysis of necropsy material over a six-year period, from 1947 to 1953. During this time a total of 871 complete necropsies, including gross and microscopic examination, were performed by the author or by resident physicians in training in pathology under the supervision of the author. In this total, there were 100 consecutive and unselected cases of coronary heart disease in which the cardiac disability was of major importance as a cause of death. There were many other cases in which coronary heart disease to a moderate or severe degree was present but some other important pathologic condition took precedence, for example, cancer. Such cases are not included in this total of 100. The study indicates to some degree the magnitude of the coronary heart disease problem in a community of approximately 50,000 population at an altitude of 6,200 feet.

CLINICOPATHOLOGIC PATTERNS

Since death in any disease is ultimately due to cardiac failure, special care in interpretation of the character of death was essential in this group of primary cardiac disease. Abrupt and unexpected death was a clinical feature in 57 cases. A review of other clinicopathologic findings in the entire series of fatal coronary heart disease revealed at least six fairly clear-cut patterns. In a number of cases there was some overlapping. Such cases were classified according to the predominant feature.

I. Orthodox—Occlusion With or Without Infarction.—In this group there were 54 cases, the majority ending in sudden death. Many were admitted with evidence of myocardial infarction and survived for several days up to one week, then died abruptly, presumably from ventricular fibrillation or extension of the original thrombus, as no new thrombi were found. Necropsy revealed eight deaths to have resulted from cardiac rupture. Other patients were dead on admission or died within a few hours after entry. In this group of 54 cases a fresh coronary arterial thrombus or hemorrhagic lesion associated with an atherosclerotic plaque was found with or without myocardial infarction. Since this clinicopathologic pattern is so well known, no example will be given.

II. Infarction Without New Occlusion.—There were 14 cases in which the clinical history and electrocardiogram indicated myocardial infarction and at necropsy fresh infarction was found. The coronary arteries showed generalized arteriosclerosis, sometimes with old occlusion and narrowing, but no fresh thrombus or

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hemorrhagic occlusion could be found to account for the fresh infarction. There was often accompanying old myocardial fibrosis. An abstract of a typical case is presented here.

A 73-year-old white woman was admitted to the hospital on March 1, 1953, with the chief complaints of nervousness, nausea, and vomiting over the past 24 hours. The patient had been under the care of a physician for many years because of hypertensive heart disease, and her blood pressure had ranged between 180 to 220 systolic over 120 diastolic. Her present illness began on Feb. 28, when she became nauseated and had a moderately severe pain in the upper portion of the abdomen and right portion of the chest. The pain radiated to both arms but not to the back. She vomited what food had been in her stomach and then continued to vomit any water which she took by mouth. She was seen by her physician at midnight, and at that time the emesis was bile-stained. Her blood pressure at that time was 180/100; pulse rate, 100 per minute and regular, and the sounds were normal. She was seen again the following morning, was still vomiting and quite exhausted, and consequently was admitted to the hospital. Physical examination revealed the heart sounds to be of normal intensity, with an occasional extrasystole. The lungs were clear. The abdomen was slightly distended and moderately rigid in the upper right quadrant. Laboratory work on admission revealed the following: Urine specific gravity was 1.030, with 2 to 3 WBC per high-power field and a very faint trace of albumin. The blood cell count showed a white cell level of 16,400 per cubic millimeter, with 79% segmented polymorphonuclear cells, 8% stab cells, 7% lymphocytes, and 2% monocytes; RBC, 5,400,000; hemoglobin, 94%. Chest x-ray showed some clouding of the bases of the lungs. On March 6, while sitting in a chair, the patient went into shock and developed cold perspiration, and the blood pressure now was 87/60. An electrocardiogram taken that day indicated left ventricular preponderance, with ST changes in Leads III, IV, and V which were interpreted as indicative of gradual myocardial infarction. She died in her sleep at 11:00 p. m., on March 8, 1953.

TABLE 1.—*Clinicopathologic Patterns*

	Cases, No.
Orthodox-occlusion with or without infarction	54
Myocardial infarction without occlusion	14
Subacute or chronic congestive failure	12
Abrupt death; no new occlusion or new infarction found	11
Clinical features of fresh infarction; none found	6
Death characterized by cerebral embolic or thrombotic episodes	3

At autopsy, the most important findings were in the heart, with evidence of mixed old fibrosis and acute and subacute infarction in the anterior portion of the left ventricle and interventricular septum. Microscopically, necrotic myocardial fibers were apparent and there was fairly dense infiltration by polymorphonuclear leucocytes. Although the coronary arteries showed a marked degree of arteriosclerosis, with calcification and narrowing, there were no areas of complete occlusion. Incidental findings included a lobular pneumonia of lipoid character, probably due to aspiration and affecting the right middle lobe.

III. Subacute or Chronic Congestive Failure.—In this group there were 12 patients who gave a history of a varying number of attacks of angina pectoris or clear-cut episodes of myocardial infarction verified by previous electrocardiograms. They were either admitted with varying degrees of edema, ascites, effusion, and dyspnea or were never able to leave the hospital after myocardial infarction because of such evidence of persistent congestive failure. Some of these died abruptly. No fresh thrombi or hemorrhagic occlusions were found, but at necropsy there was found extensive coronary arteriosclerosis, often with old or subacute organized thrombi or old occlusions due to atherosclerotic plaques. The myocardium showed varying degrees of fibrosis or discrete zones of old infarction. There were no fresh

infarcts. An interesting feature of this group was the relative old age. Of these 12 patients, 8 were 70 years of age and older, 4 being 80 years of age and older. An abstract of the clinicopathologic features of a typical case follows.

A 72-year-old white man entered the hospital on April 30, 1950, too ill to furnish a detailed history. It was learned from his wife that four nights previously he had been awakened from sleep by severe epigastric and substernal pain radiating into the shoulders. He vomited once and had diuresis throughout the night. He did not call a physician until two days later, when the chest discomfort became associated with progressive shortness of breath and cyanosis.

Physical examination revealed, among the important findings, that the cardiac rhythm was regular, the rate 92 per minute, and the heart somewhat displaced to the left, with a friction rub audible over the left lateral border. The blood pressure was 102/82, respirations 32 per minute, and temperature 101.4 F. Electrocardiographic changes were indicative of posterior and left lateral myocardial infarction. The pertinent results of laboratory studies were as follows: Sedimentation rate was 25 mm. in an hour; WBC, 15,350 per cubic millimeter, with 78% polymorphonuclear cells; Kahn reaction, negative, and urine specific gravity, 1.020, with microscopic and chemical examinations showing no abnormalities. The patient was treated with oxygen by nasal catheter; he was given anticoagulants, including meperidine (Dicumarol) and depoheparin; sedatives, and, later, small doses of quinidine to control paroxysms of ventricular tachycardia. The clinical course seemed favorable at times but alternated with periods in which the patient developed attacks of cyanosis, chest discomfort, perspiration, cough, shortness of breath, nausea, and apprehensiveness. During such times the pulse became rapid and weak, and physical examination revealed evidence of pulmonary edema and congestion. On Dec. 4, 1950, slightly more than three months after entry, he developed nausea, chest tightness, cough with frothy mucus, cold sweats, and a weak rapid pulse. He died quietly.

Necropsy revealed an old occlusion of the right main stem and subacute thrombosis of the left circumflex branch. There was an extensive subacute infarction of the left lateral posterior ventricular wall. Pulmonary edema and congestion and bilateral pleural effusions were found also.

IV. Abrupt Death; No New Occlusion or New Infarction Found.—Eleven cases were found in this group. The clinical evidence indicated old coronary heart disease, and death occurred suddenly. The majority of these patients were found dead by a nurse in the hospital or by the family at home. To establish a distinction between this group and those cases dying abruptly in Group I, there was an interval of at least two weeks and usually many months since previous infarction. No new thrombi were found, and the deaths were considered due to ventricular fibrillation. These cases also differed from those described above in Group III in that there was no evidence of subacute or chronic congestive failure, i. e., edema, ascites, or effusion. An abstract of the clinical history of a typical case is presented here.

A 49-year-old white man entered the hospital for the first time in 1946 with history and EKG findings typical of anterior myocardial infarction. The patient made a satisfactory recovery and returned to work. In 1948, the patient was found to have diabetes and gallbladder disease. He seemed to get along fairly well on a dietary regime until April 8, 1952, when he was readmitted to the hospital complaining of irregularity in his heart beat. The patient had been treated as an outpatient for cardiac irregularity by digitoxin (Purodigin) and quinidine. An EKG taken shortly before entry showed no extension of the infarcted zone in comparison with the one taken in 1946. Physical examination revealed a ruddy obese white man, with other pertinent findings including a Grade 2 sclerosis of the retinal vessels; blood pressure 140/120, and a Grade 3 harsh systolic murmur over the apex. Laboratory studies disclosed the following: Urine specific gravity was 1.011, with 3+ albumin and 4+ glucose; there were occasional WBC and RBC and a negative Kahn reaction. The patient developed evidence of acute cholecystitis. An operation was performed on April 14, 1952, and the gall bladder was drained. He made a

spontaneous recovery until April 24, 1952, when he developed jaundice and the drainage from the cholecystostomy seemed to increase. On May 26, 1952, the patient showed evidence of complete heart block. However, both conditions improved, and the patient was discharged from the hospital on June 9, 1952. He got along fairly well at home but died abruptly on the morning of June 16, 1952, and was brought back to the hospital for necropsy.

At autopsy severe generalized coronary arteriosclerosis was found, with old occlusion of the left anterior descending branch. The occlusion was associated with an old area of infarction in the left ventricular wall anteriorly and also extending over the anterior portion of the interventricular septum. The process was associated with aneurysm formation. No fresh occlusion was found. Other findings included chronic generalized pancreatitis with stone formation. Death had resulted from abrupt cardiac failure.

V. Final Attack Suggestive of Fresh Infarction; None Found.—In this group there were six cases with clinical features of a myocardial infarct, i. e., substernal pain, collapse, cold perspiration, and survival for four hours or more. An abstract of a typical case follows:

A 40-year-old white man was admitted to the hospital for the last time on Aug. 30, 1952. Past history revealed that the patient had suffered a heart attack in February, 1952, and was hospitalized at that time. During that entry he complained of pain in the chest of two weeks' duration, which disappeared and recurred on a number of occasions. The pain was usually sharp in character but not of great severity except on exertion. He seemed to be relieved by fresh air, and he thought the pain was due to smoking or possibly "flu." However, three nights prior to his admission in February, 1952, he had a severe attack of precordial pain, coming on during his sleep and lasting about 15 minutes with some sweating. Physical examination at that time revealed a regular pulse with a rate of 72 per minute and a respiration rate of 18 per minute. Blood pressure was 140/100. The patient was a well-developed and well-nourished white man in no particular distress. The chest examination revealed the heart tones to be good, with no murmurs and no rubs. The lungs were clear to percussion and auscultation. Examination of the abdomen revealed the liver to be down 4 cm. in the midclavicular line. An EKG showed evidence of a left lateral wall infarction, with the picture changing somewhat later, on another EKG, to include the anterior wall. Blood studies revealed WBC 7,850 per cubic millimeter, with a differential count of 62% polymorphonuclear cells and 38% lymphocytes, and hemoglobin 15.5 gm.; Kahn reaction was negative; urinalysis was not remarkable. The patient was treated with meperidine and made a fairly good recovery, except on March 18, when he developed a sudden attack of left hemiparesis. The neurologic condition cleared, and the patient was discharged on March 31, 1952. His final entry was on Aug. 30, 1952, when the history revealed that 1:00 p. m. he had developed severe chest pain accompanied by partial collapse. Physical examination revealed a blood pressure of 130/80, and the heart tones were markedly irregular in character. The neck veins were slightly distended, and there were a few basal rales. An EKG at this time was interpreted as showing fresh infarction, probably posteriorly and septal, with anterior subendocardial extension. The patient was treated by oxygen by mask, heparin, and digitoxin. He died shortly after 5:00 p. m., on the day of admission.

At autopsy the coronary arteries showed generalized severe arteriosclerosis, with subacute occlusion of the left anterior descending branch and old incomplete occlusion and recanalization in the right main stem. Myocardial infarction of subacute character was present in the anterior wall of the left ventricle and anterior portion of the interventricular septum. Multiple sections of the posterior wall of the left ventricle, posterior wall of the interventricular septum, and posterior wall of the right ventricle showed no evidence of acute or subacute infarction, grossly or microscopically. There was also no evidence of fresh thrombosis or occlusion.

VI. Death Characterized by Cerebral Embolic or Thrombotic Episodes.—In this group there were three patients in whom the clinical evidence indicated a cerebrovascular accident and coronary arterial heart disease was found, either clinically or after death or both. In this group recent or subacute myocardial infarction and

mural thrombosis were found. The cerebral episode was considered to be either embolic or thrombotic. An abstract of the clinicopathologic features of a typical example follows:

A 61-year-old white man entered the hospital on Sept. 9, 1947, with a complaint of high midline abdominal pain for the previous three weeks. The pain occurred in attacks lasting from 5 to 10 minutes, and the patient was relieved by slowing up at his work. The frequency and severity of the attacks increased and reached a climax on the night of Sept. 8, 1947. At that time the patient had a severe seizure, with substernal pain radiating into the shoulders and down both arms. On admission the patient was perspiring freely, moderately cyanotic, anxious, and complaining of substernal pain. The pulse rate was 80 per minute and regular. The blood pressure was 140/110. The chest was clear, and the heart rate was regular, but there was a loud friction rub over the apex. An electrocardiogram showed extensive T_4 changes, and a diagnosis of coronary occlusion with myocardial infarction was made. The patient was given oxygen, morphine, and pentobarbital (Nembutal). The response was satisfactory, and the friction rub disappeared. The blood pressure, pulse rate, and respirations remained steady. On Sept. 17, 1947, however, the patient developed cyanosis and complained of numbness of the left side of the face. Physical examination revealed dilatation of the left pupil, weakness of the left facial musculature, and paresis of the left arm, left hand, and left lower extremity. The patient was placed on bishydroxycoumarin (Dicumarol) at this time. On Sept. 23, 1947, pulmonary edema developed, with elevation of pulse rate and increased dyspnea. The patient died on Sept. 27, 1947.

TABLE 2.—*Age and Sex Distribution*

	Males	Females
Under 40	2	0
40-49	10*	0
50-59	22	4*
60-69	20	3*
70-79	19*	10****
80-89	5	5
Total	78	22

* Each asterisk indicates a diabetic.

At necropsy, the heart revealed recent thrombosis of the left anterior descending coronary artery, with secondary myocardial infarction, and an aneurysm in the infarcted left anterior ventricular wall. A partially organized mural thrombus was present in the chamber of the left ventricle and was believed to be the source for cerebral emboli. A fairly fresh infarct was observed in the right occipital and right temporal lobes of the brain.

OTHER CLINICOPATHOLOGIC FEATURES

(a) Age and Sex Distribution.—In the total of 871 necropsies, 645 patients were 40 years of age or over, and in this group 98 cases of fatal coronary heart disease were found. There were two cases of fatal coronary disease in patients under 40 years of age, both in males. Of the 100 cases, 78 were males and included 2 diabetics and 22 were females, of whom 6 were diabetics. A striking feature of the sex distribution, as shown in Table 2, was the relatively benign character of this disease in females. The number of cases in females is reduced to only 16 if the 6 diabetics are eliminated, and 11 of those 16 were 70 years of age or older.

(b) Complications.—In 15 hearts of the entire series of 100 fatal cases of coronary heart disease there was mural thrombosis. The mural thrombosis was associated with emboli in five. In eight hearts rupture and hemopericardium had

occurred. Myocardial aneurysm developed in 12 patients, and in none of these had rupture taken place. Mural thrombosis was present in 4 cases of this group of 12 myocardial aneurysms.

(c) Character of the Coronary Arterial Occlusion.—The left anterior descending branch was involved in 58 hearts. The next most frequent vessel involved was the right main stem, affected in 30. The left circumflex was involved in 25. Multiple vascular occlusions had occurred in 27, and in 15 cases no definite recent or old occlusion could be demonstrated, although the latter group often showed marked narrowing of the coronary vessels. In the majority of cases a thrombus was responsible for the occlusion. Grossly it was sometimes difficult to differentiate antemortem from postmortem thrombi. Hemorrhage into an atherosclerotic plaque occurred much less frequently than thrombosis. Occasionally, the occlusion was due to atherosclerotic changes alone, with no evidence of thromobosis or hemorrhage. In old thrombi which had been secondarily organized and recanalized, gross differentiation between arteriosclerotic narrowing and incomplete organized thrombosis was difficult. Calcified arteries were difficult to examine histologically when they contained small friable fresh thrombi. It was sometimes impossible to decalcify the specimen without dislodging most of the friable thrombus.

(d) Myocardial Infarction.—In this series there were 36 cases of fresh myocardial infarction diagnosed grossly at necropsy and verified microscopically. Many of these were mixed with older areas of fibrosis. In 11 additional cases, independent of the 36, microscopic evidence of myocardial injury as manifested by polymorphonuclear leucocyte infiltration with or without myocardial necrosis was found. The duration of life following the onset of precordial pain in the 36 patients with infarcts diagnosed grossly varied between 13 hours and 23 days. In the 11 cases which presented microscopic evidence only of myocardial injury the duration of life following the onset of precordial pain varied between 15 minutes and 48 hours. In 2 cases of the 36 gross infarcts the history was vague and precordial pain was absent or mild; hence these 2 could be considered examples of "silent" infarction. In 1 out of the 11 cases diagnosed microscopically, "silent" myocardial injury was diagnosed, for the same reason.

(e) Survival Time Following Onset of Final Fatal Occlusion.—There were 62 cases of final fatal occlusion with or without infarction, and the survival time following the clinical onset of the fatal occlusion varied as follows: Eight patients died within less than an hour; 4 patients survived to less than 13 hours; 10 survived from 13 to less than 25 hours; and 40 lived 25 hours or longer, with more than half of the deaths during the first week and the longest survival time in this category being 23 days.

(f) Precipitating Factor in Abrupt Death.—There were 57 abrupt deaths in this series. The clinical chart was analyzed in each case for a possible precipitating factor. In the physician's progress or nursing notes of 41 patients there appeared to be no cause, and the patient was apparently resting in bed or in his room and not exerting himself. In five patients abrupt death followed a trip to the bathroom or use of the bedpan. In four patients it was related to a "full or heavy" meal. In four patients abrupt death followed a period of restlessness and disorientation. Some of

these patients were found wandering in their rooms or walking in the halls despite medical orders of bedrest. Finally, in three patients there was a history of some type of physical activity or exertion.

(g) Survival Time Following First Diagnosis of Coronary Disease.—The total duration of the disease, as far as could be determined from the subjective complaints, varied as follows: Thirteen patients survived 24 hours or less; 25 patients survived over 24 hours and less than 1 month; 19 survived from 1 month to less than 1 year; 22 survived from 1 year to less than 5 years; 7 survived from 5 years to less than 10 years; 2 survived 10 to 15 years. In 12 cases the total duration of the disease could not be accurately determined. It was difficult or impossible in some histories to separate digestive upsets, "heartburn," and arthritic or neuralgic pains from true angina pectoris.

COMMENT

The subjects of sex incidence of coronary arterial disease and the relation to diabetes mellitus require no comment. They have been repeatedly emphasized by others.

In taking the clinical history it was exceedingly difficult to identify past attacks of angina pectoris in patients who had not sought medical attention at the time and in whom there was no electrocardiographic or recorded clinical evidence during the attack. Cases of angina pectoris, actual coronary occlusion and myocardial infarction, and digestive upsets could not be differentiated from the patient's history alone. The family physician would sometimes come to the necropsy room and expect a demonstration of several occluded coronary vessels and multiple myocardial infarcts. Only one would be found. The reverse necropsy finding of multiple occlusions where one was expected was not infrequently found also.

Cases listed in Group V above, i. e., "final attack suggestive of fresh infarction; none found" were a source of dissatisfaction to both clinician and pathologist. The clinical picture was suggestive or diagnostic of myocardial infarction. The electrocardiographic findings were considered suspicious or diagnostic of infarction. Neither fresh thrombus nor infarct could be demonstrated at necropsy, although older processes of this type were found. Frequently the clinician attended the postmortem examination in such cases, and many extra sections of the myocardium were taken at his request from suspicious gross areas where the clinician felt microscopic evidence of injury might be found. Although it was thought that postmortem injection studies [1] in such cases might have disclosed areas of occlusion missed by dissection with small sharp-pointed scissors, the possibility of missing occluded vessels large enough to produce the clinical picture was rejected by the pathologist. The pain was believed due to widespread coronary arterial spasm and myocardial ischemia, but other factors, such as a low pain threshold or a change in the patient's threshold, were considered also.

Myocardial aneurysm developed in 12 patients. None of these had ruptured. There were eight hearts in this series wherein rupture and hemopericardium had occurred. The person with myocardial aneurysm would appear to be in no greater danger of cardiac rupture than the person who is free from this complication. Rupture in the eight hearts was unrelated to myocardial aneurysm.

The pathologist is often asked the question at clinicopathologic conferences about how long it takes following occlusion for infarction to develop. This question is

difficult to answer, because it is dependent upon the assumption that the onset of precordial pain is indicative of the onset of coronary occlusion. In this series, furthermore, there were three cases of "silent" myocardial infarction. In many other patients, admitted in critical condition, it was difficult to obtain the exact time of onset of symptoms. The family physician usually did not press this point, for obvious reasons. The word of relatives in this regard was not always reliable, as some patients kept their symptoms to themselves for some time before informing immediate relatives, particularly when the household was asleep. Experimental evidence in animals based upon arterial ligation methods is not applicable to the situation in human coronary occlusive disease, because the degree of arteriosclerosis in the nonoccluded vessels [2] and the presence of anastomotic channels play an important part * in recovery of the myocardium. In this series the shortest survival time following the onset of precordial pain and with gross evidence of myocardial infarction at necropsy was 13 hours. It should be pointed out, however, that of the 62 cases of final fatal occlusion only 12 fell in the group surviving less than 13 hours. Thus, approximately one fifth only of the cases could be used in attempting to answer this question. It is the opinion of the author that gross myocardial change is apparent before 13 hours. Microscopic evidence of myocardial injury, as manifested by polymorphonuclear leucocyte infiltration, was present as early as 15 minutes from the onset of the fatal attack of precordial pain.

The subject of survival time was divided into two parts: Survival time following the onset of the final fatal attack and survival time following the first diagnosis of coronary arterial disease. In regard to the first group it should be mentioned that many persons dying suddenly from coronary arterial disease never reached the hospital and were taken directly to a mortuary. A few of these were brought into the hospital later for necropsy. It was noted that if a patient survived more than 1 hour he would usually survive more than 12 hours. However, after that and for the remainder of the first week the greatest number of fatalities occurred. The remainder died during the second and third weeks, with the longest survival time 23 days.

Survival time following the first clinical diagnosis of coronary arterial disease varied between extremes of just one attack and death a matter of a few minutes or hours after the attack and a history of multiple attacks extending up to a period of 15 years. Since this series is only concerned with those doomed to die of coronary disease, the figures are prejudiced on the pessimistic side. For a balanced outlook based on a series including survivors, the study by Bland and White [4] of 200 cases showed 25% survival for more than 10 years. In rather sharp contrast, only 2 patients of this series of 100 fatal cases survived over 10 years.

An analysis of the clinical records for precipitating factors in the 57 abrupt deaths provided little helpful information. In the great majority of cases, 41, there was little or no activity. Most of these patients were in bed and apparently resting. The remaining 16 were engaged in ambulant hospital or other activities in which the question of better clinical control might or might not have been raised. Most physicians treating a patient with arteriosclerotic heart disease appear alert to the subject of myocardial work. In addition to prescribing bedrest they appreciate that increased myocardial work occurs during digestion, defecation, and emotional stress.

* References 1 and 3.

They act promptly with diet, laxatives, and sedation to prevent or correct abdominal distention, constipation, straining at stool, apprehension, tension, and pain. Since 1951 the use of anticoagulants in coronary disease has been almost routine in these two hospitals.

SUMMARY

Clinicopathologic analysis is presented of 100 consecutive and unselected cases of fatal coronary heart disease with complete necropsy examinations.

Although some overlapping occurs, at least six clinicopathologic patterns are identified.

Other features, such as aneurysm formation, rupture, character of the occlusion, time required for myocardial infarction, survival time, and precipitating factors in abrupt death, are presented and discussed.

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NITROGEN MUSTARD IN TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS

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LOS ANGELES

CHASIS, Goldring, and Baldwin in 1949 reported on the favorable use of methyl-*bis* (β-chloroethyl) amine hydrochloride (nitrogen mustard) in glomerulonephritis.[1] Their rationale for using this drug was based on "the assumption that human glomerulonephritis is the result of tissue alterations in the kidneys induced by an antigen-antibody complex."[2] Nitrogen mustard is known to inhibit antibody production. Several confirmatory reports of the use of the agent in the nephrotic syndrome have appeared in the literature.* In a recent paper Baldwin, McLean, Chasis, and Goldring stated that the evidence favoring the use of nitrogen mustard in human glomerulonephritis is equivocal.[2] Dustan, Corcoran, and Haserick first used this drug in systemic lupus erythematosus with renal involvement.[5]

Rohn and Bond administered nitrogen mustard to five patients who had systemic lupus erythematosus without renal damage. Three cases were benefited.[6]

Since Duston's preliminary report, in 1951, we have treated 20 patients with active acute and subacute systemic lupus erythematosus with 34 courses of intravenous nitrogen mustard and 11 courses of oral triethylene melamine (TEM). Five patients received the oral form of TEM. In the total group there were 11 edematous patients with the nephrotic type of nephropathy, and 8 of these were helped. Two patients with lupus nephropathy without edema were not benefited. None of the seven other patients without clinical evidence of renal damage were aided in any way. Two of the five subjects given TEM developed agranulocytosis, one case of which progressed to a fatal aplastic anemia. Both patients had normal white blood cell counts at the start of therapy and prior to their subsequent doses of the drug.

MATERIALS AND METHODS

Intravenous methyl-*bis* (β-chloroethyl) amine hydrochloride (Mustargen) was usually administered in a single dose of 20 mg. injected into the tubing of an intravenous infusion of 5% dextrose in water. This amount approximated 0.4 mg. per kilogram. The drug was given during the evening after premedication with 0.1 gm. of phenobarbital and 0.1 gm. of pentobarbital sodium. Since there is no evidence of increased toxicity when nitrogen mustard is given as a single dose instead of divided over several days, this is the preferable manner of giving the drug.

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Methyl-*bis* (β-chloroethyl) amine hydrochloride (Mustargen) was supplied by Dr. E. Alpert, of Merck & Company, Inc., Rahway, N. J. Triethylene melamine was provided by Dr. J. M. Ruegsegger, of Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

* References 3 and 4.

Triethylene melamine, in 5 gm. tablets, was taken with water on an empty stomach one hour before breakfast. Initial courses consisted of a total dose of 10 to 15 mg. over a two- to three-day period. Hemoglobin and white blood cell counts were normal prior to each dose. The interval between courses was not less than two weeks.

Addis counts were performed, by the technique recommended by Ham, on 12-hour overnight urine specimens.[7] Urinary protein determinations were made with Tsuchiya's reagent according to Addis' method and reported as output per 24-hour period.[8] All patients were on cortisone or corticotropin (ACTH) at the time of administration of the nitrogen mustard or TEM, since it is believed that these steroids are the mainstay of therapy.[9]

CLINICAL PATTERN OF RENAL DAMAGE

Before discussing the results obtained, which were favorable only in those patients with overt renal damage, it is worth while reviewing the course of systemic lupus, which is fundamentally the same whether modified by steroid therapy or not. Apparently, hormonal treatment prolongs lives and tides many acutely ill and moribund patients over almost certain fatal crises but it does not change the pattern of the disease or increase the incidence of nephropathy. About 40% of the treated patients eventually enter remissions after their first attack, and cortisone or corticotropin therapy can be stopped. The remainder must remain on the drug for prolonged periods. In both the treated and untreated patient the renal lesion develops in a similar manner. There are three ways in which evidence of renal involvement appears. The commonest is an insidious rise in blood pressure, which is not altered by either reducing or stopping hormonal therapy. The urine is usually normal at first, and then in progression there appear albuminuria, a few white cells, red cells, granular and red cell casts, and eventually fat bodies and broad casts. These changes appear over the course of months rather than over the years that it takes them to occur in chronic glomerulonephritis. About the time that the urine begins to show changes the serum cholesterol level rises. In the second group of patients the blood pressure remains normal or at the upper limit of normal while progressive albuminuria develops with the gradual appearance of the above "telescoped" urinary sediment. The third type is the development of pyelonephritis and cystitis, which is intractable in many cases. Careful studies of the urinary sediment in these patients show the picture of the elements described above in addition to the superimposed infection. Often a rising blood pressure is noted at this time. Although pyelographic studies are normal, the bacterial infections are usually resistant to the proper antibiotics. The nonprotein nitrogen and renal function are abnormal in the acutely ill lupus patient in crisis and in the terminal stages of lupus nephropathy; otherwise, despite a markedly pathologic urine, the kidney function is not greatly impaired, as determined by the usual tests. Since cortisone benefits the early renal damage but does not prevent in all cases the progression of the disease, it was hoped that nitrogen mustard might ameliorate the renal damage, if present, and possibly also induce a remission in the underlying disease process in those patients without nephropathy whose lupus was very active despite high doses of cortisone over long periods.

CLINICAL RESULTS

All 20 patients had active acute and subacute systemic lupus erythematosus which was going progressively downhill despite cortisone maintenance. In order to classify the results into an intelligible pattern the patients were divided as outlined in Table 1. It is apparent that the best results were obtained in the edematous patient

with the nephrotic type of nephropathy. Nitrogen mustard is also effective in edematous nephroses due to other causes.† The greater the degree of edema the more spectacular the result, as shown in Table 2. Most of these patients were not responsive to mercurials administered with ammonium chloride. Within 3 to 14 days after administrations of nitrogen mustard a diuresis began in three of the five patients with severe anasarca. One of the patients, who did not respond to any diuretic and had been waterlogged for five months, lost 34 lb. (15.3 kg.) by diuresis during the 10-week period following administration of the drug. Within a few weeks after the administration of nitrogen mustard in these patients the serum proteins returned to normal and the urinary sediment improved, except in the one terminal case. The dosage of cortisone was not altered for several weeks prior to nitrogen mustard therapy or during the period of improvement. Four of the six relatively dry nephrotic patients were generally improved after treatment, and their urine albumin and sediment values returned toward normal. There seemed to be less activity of their rash, arthritis, etc. Two patients had hypertension with nephropathy but without edema. One was moribund on administration of the drug and died 10 days later. The other was not benefited. No improvement was noted in seven patients without overt renal damage. There was no effect on their skin lesions, joint pains, required maintenance dose of cortisone, hypertension, or other changes, in contradistinction to the finds of Rohn and Bond, who report that this drug can ameliorate the disease in patients without renal changes.

In no patient in this series was a full remission induced by nitrogen mustard so that cortisone therapy could be stopped. Hypertension, even in patients who had a good diuresis, was only temporarily benefited, if at all.

CHANGES IN LABORATORY FINDINGS

The proteinuria decreased in 10 of the 13 patients with renal damage, from as much as 40 gm. per 24 hours to 1.5 gm. (Patient V. S.). The urinary sediment improved in seven patients and returned to normal in four of the seven cases. The serum albumin rose and globulin decreased in two of the three edematous patients on whom adequate determinations were performed. The serum proteins in the relatively dry nephrotic group were normal at the onset of therapy. The nonprotein nitrogen decreased in two of the three patients in the first group in whom it was elevated and in all three who had abnormal levels in the second group. The highest level was 90 mg. per 100 cc., and this fell to 51 mg. per 100 cc. several weeks after treatment. Phenolsulfonphthalein tests usually showed good secretion, except in the terminal case. The serum cholesterol was serially studied in three patients, and it only changed in one patient, from 388 to 92 mg. per 100 cc.

TOXICITY OF NITROGEN MUSTARD BY MOUTH AND INTRAVENOUSLY

The only reactions noted from the intravenous form of nitrogen mustard were nausea and vomiting in about 80% of the patients and occasionally a localized phlebitis. Seven to 10 days after administration of the agent a transitory leucopenia appeared for about a week. Prophylactic antibiotics were not administered when the leucocyte levels were low. No patients develped agranulocytosis.

† References 3 and 4.

TABLE 1.—*Results of Nitrogen Mustard Treatment of Twenty Patients with Systemic Lupus Erythematosus*

Group	Patients, No.			Remarks
	Total	Improved	No Change	
Edematous, nephrotic	5	4	1	The patient who had no change was almost terminal prior to nitrogen mustard administration and died two weeks later
Relatively dry nephrotic	6	5	1	
Hypertension with nephropathy without edema	2	..	2	One patient terminal on administration of nitrogen mustard
Hypertension without overt renal change	2	..	2	
Active disease with normal renal function	5	..	5	No effect on rash, arthritis, or other pathological changes in this group

TABLE 2.—*Results of Nitrogen Mustard Therapy*

		Dose/ Course, Mg.*	Weight, Lb.†	Urine Albumin‡	Sediment	Activity of the Disease	Over-All Result
Edematous, nephrotic							
E. P.	9/ 5/53	20	152 → 118	8.7 gm. → 6.0 gm.	Improved	Less	Good diuresis, resistant Pyelonephritis, remission
R. C.	8/28/52	20	146 → 123	4+ → Tr	Improved	Less	Good diuresis, remission
	12/18/52	20	139 → 146	2+ → Tr	Improved	Less	No effect
	5/19/53	20	154 → 146	4+ → Tr	Improved	Less	Good diuresis
G. F.	1/21/52	10	122 → 104	4+ → 2+	No change	Less	Good diuresis
	3/12/52	20	117 → 107	3+ → 1+	No change	Less	Good diuresis
B. R.	7/15/51	20	121 → 121	3+ → 3+	No change	No change	No change
	1/11/52	10	139 → 139	7.0 → 7.0	No change	No change	No change
	1/18/52	10	139 → 139	7.0 → 7.0	No change	No change	No change
	1/29/52	10	139 → 139	7.0 → 7.0	No change	Less	Improved
	3/ 6/52	20	140 → 140	3+ → 3+	No change	Less	Improved
	11/29/52	20	130 → 130	2+ → 2+	.....	Less	Improved
	12/10/52	10	130 → 130	2+ → 0.3	Improved	Less	Improved
J. V.	12/ 3/52	20	110 → 110	4+ → 4+	No change	No change	Terminal when treated
Relatively dry nephrotic							
V. S.	3/12/53	20	122 → 122	40 → 1.5	No change	Less	Improved
	8/ 7/53	20	127 → 127	7.2 → 3.6	No change	Less	Improved
B. S.	1/ 7/53	TEM 15	117 → 110	0.8 → 0.5	Improved	Less	Improved
	1/21/53	TEM 10	110 → 110	0.8 → 0.5	Improved	No change	No change
L. C.	4/29/53	10	130 → 130	7.0 → 2.3	Improved	Less	Improved
A. C.	10/31/52	20	143 → 143	0.75 → 0.46	Improved	Less	Improved
	12/ 5/52	20	143 → 143	Tr → Tr	No change	No change	.....
	12/16/52	10	143 → 143	Tr → Tr	No change	No change	.....
	1/ 7/53	TEM 15	152 → 152	1+ → 0	Improved	Less	Improved
	6/12/53	20	162 → 162	1.9 → 0.64	Improved	Less	Improved
M. A.	1/ 6/52	10	88 → 88	4.0 → 4.0	No change	Less	Improved
	1/21/52	10	87 → 83	4.0 → 1.5	Improved	Less	Improved
	6/24/52	15	73 → 76	2+ → Tr	Normal	No change	No effect
	7/10/52	10	76 → 67	1+ → 2+	Normal	No change	Good diuresis
B. B.	5/ 1/53	12	140 → 140	2.8 → 0.7	Improved	No change	No effect

* Dose is nitrogen mustard intravenously unless specified.

† Figures are weights immediately prior to the drug and minimum attained several weeks later.

‡ Urine albumin in grams per 24 hours or + units. Amounts are excretion prior to nitrogen mustard therapy and minimum reached several weeks to months later.

Two of the five patients given TEM by mouth had nausea. One patient had a transitory leucopenia 10 days after a total dose of 25 mg. given as two courses a month apart. Another had no leucopenia after one dose of 15 mg. A third patient had no change in her leucocyte level after 25 mg. given over a five-week period. The fourth patient had a normal hemoglobin level and white cell count two weeks after a 15 mg. dose and then was given an additional 10 mg. Three weeks later the white cell count fell to 300 and platelets disappeared, with hemorrhagic phenomena. After vigorous antibiotic and cortisone therapy she recovered. The fifth patient received 15 mg. without any change in her hemogram and two weeks later received another 10 mg., again with no fall in her blood cell count. Five weeks after this dose, again with normal white cell count, she received 15 mg. more, and two weeks later her leucocyte level was 3,100. She died of aplastic anemia six weeks after the last dose of TEM, despite massive amounts of antibiotics and cortisone. It is possible that lupus patients are more sensitive to the effects of TEM, even when their hemograms are normal. However, because of its erratic toxicity others as well as we have stopped using the drug in various disease states.

COMMENT

Nitrogen mustard seems to be of value in treating the edematous and relatively dry nephrotic syndromes of lupus nephropathy. It should be administered to the patient only after the condition has been ameliorated as much as possible by cortisone, since this drug will help early renal damage in lupus.[9] Untreated critically ill lupus patients may have nonprotein nitrogen levels as high as 130 mg. per 100 cc., with abnormal urinary findings, and these changes can be corrected fully by hormonal therapy. If renal damage and edema persist after a month or more of this form of therapy despite the use of a low-sodium diet and mercurials, then it is worth while trying nitrogen mustard. The intravenous form only should be administered, because of the unpredictable toxicity of orally administered TEM.

SUMMARY

Twenty patients with active systemic lupus erythematosus on maintenance cortisone dosage have been treated with the intravenously and orally administered forms of methyl-*bis*(β-chloroethyl) amine hydrochloride and triethylene melamine (TEM). Four of five very edematous patients with the nephrotic syndrome of lupus nephropathy had good results, with diuresis appearing in three of these five within 3 to 14 days after administration of the drug. These patients had been resistant to mercurials. The fifth patient was in a terminal state when the drug was administered. Five of six relatively dry nephrotic patients had improvement in their renal and over-all status as well. Two patients with hypertension with nephropathy and no edema were not benefited. When improvement occurred, the albuminuria, urinary sediment, serum protein values, and the over-all clinical picture were better. Hypertension was unaffected, however. None of the seven patients without evidence of renal damage were benefited.

Triethylene melamine was administered by mouth to five patients in 11 courses. Agranulocytosis occurred in one case and fatal aplastic anemia in another, despite the usual precautions being employed in giving this drug. TEM is too toxic

for use in lupus erythematosus, because of its unpredictable behavior. No serious toxicity has been noted from the 34 courses of intravenously administered nitrogen mustard.

ADDENDUM

Since this paper was written, an additional four patients with the very edematous type of nephropathy have been treated with intravenous nitrogen mustard, with equally good results upon anasarca, proteinuria, urinary sediment, serum proteins and their general over-all clinical picture.

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PRIMARY AMYLOIDOSIS

Relationship to Secondary Amyloidosis and Report of a Case

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AMYLOIDOSIS is classified into groups, as primary, secondary, localized or tumor-forming, and the kind associated with plasmacytoma.[1] The clinical characteristics of each group usually are distinctive enough to set it apart, but other features suggest a closer relationship than is apparent. Clinical differentiation between primary and secondary amyloidosis is of more than academic interest. Recovery from the primary form has not been reported, and amyloidosis secondary to other disease is reversible and may disappear if the cause is removed before the process is too far advanced.[2]

Primary amyloidosis, as its name implies, is not preceded by a discernible cause. Amyloid accumulates slowly over years in and around blood vessels and in tissue of mesenchymal origin generally. The disease becomes clinically evident chiefly in middle-aged or aged persons. Similar amyloidosis occurs spontaneously in senile mice.[3]

The secondary form is encountered most frequently and occurs chiefly in young adults. It develops relatively quickly, during some chronic disease associated with hyperglobulinemia. Unless the cause is removed, amyloid accumulates in especially large amounts in the kidneys, liver, and spleen and may end in death within two years. Amyloidosis can be caused experimentally by injecting animals with agents which induce hyperglobulinemia.[4]

The distinction between primary and secondary amyloidosis is not always so clear. For example, in many cases reported as primary amyloidosis the kidneys, liver, and spleen were rich in amyloid * and others were preceded by chronic suppurative disease †; the amyloid of multiple myeloma usually is distributed like that of the primary form but is secondary to the myeloma and is related to hyperglobulinemia; secondary amyloidosis is more generalized or systematized than is usually believed.[13] Overlapping features like these confuse classification. Perhaps, as more cases are observed newly recognized details will aid in clarifying the relationship of the various forms.

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* References 5-8.

† References 9-12.

The case to be described has several characteristics of primary amyloidosis, yet the patient was a relatively young person and there is uncertainty as to the nature of the early period of a four-year illness. At necropsy, the liver and spleen were filled with amyloid and plasma cells in the marrow raised the question of plasmacytoma.

REPORT OF A CASE

Mr. M. P., aged 37, while in Naval service in 1945 had minor gastrointestinal disturbances in common with his crew mates. Except for hemorrhoids and ocasional pain in his coccyx he was generally well, donated blood on several occasions, and weighed 92 kg. (202 lb.)

In September, 1949, after strenuous exercise, there were severe aching, soreness, and stiffness of his muscles and joints, which persisted two or three weeks. A physician found his temperature to be 38.5 C. (101.3 F.). He was sent to a hospital, where chills, temperature of 40.5 C. (105 F.), and profuse sweating occurred. All diagnostic tests and cultures were unrevealing. Therapy with penicillin had no effect. The temperature diminished to normal after two weeks. He lost 12.7 kg. (28 lb.). Soon after he returned to his home, his temperature again rose to 38.5 C. (101.3 F.), for a three-week period. His joints were stiff and tender but not inflamed or swollen. He again entered the hospital in October. There was a shaking chill and the temperature rose to 41 C. (105.8 F.). Penicillin, chlortetracycline, chloramphenicol, and streptomycin were ineffective in therapy. After 12 days the patient recovered but continued to have soreness and stiffness of his muscles, wrists, and ankles. His feet were sore and painful on standing. He left the hospital but had hardly reached his home when chills and fever recurred. At this time generalized lymphadenopathy appeared. The signs and symptoms abated after several days, and he returned to his work although fever of 38.5 C. (101.3 F) persisted. Several minor operations to remove tonsillar stumps and drain the nasal sinuses were done in December, 1949, without beneficial effect.

The patient continued to work, but soreness and stiffness of his muscles were distressing. Walking was painful and difficult but improved after exercise. There was aching of the knees, wrists, fingers, and thumbs. Episodes of low fever lasted about a week and recurred at 2- or 3-week intervals. Bleeding, presumably from hemorrhoids, usually recurred during the febrile periods.

In May, 1950, because of weakness and loss of weight he entered a Veterans Administration Hospital for study. There was low fever, slight swelling of the fingers, and a sedimentation rate of red cells of 32 mm. per hour. Perhaps most important in regard to the subsequent diagnosis were occasional blood-streaked stools and an ulcerated hemorrhagic area on the nasal septum. The lymph nodes were still enlarged. All other studies were unrevealing, and no diagnosis was made.

The patient resumed his work and had occasional periods of fever, aching, and stiffness. He weighed 75 kg. (164 lb.). He returned to the same hospital in November, 1950, for a month's observation. There was fever (temperature of 37.8 C., or 100 F.) daily. All studies again failed to reveal a cause or permit a diagnosis. Aspirated sternal marrow showed no abnormal cells. The sedimentation rate (Wintrobe) was 11 mm. in 1 hour. Collagen disease, rheumatoid arthritis, lymphoma, rheumatic fever, malaria, and brucellosis were considered. Except for stiffness the patient gradually improved, and he regained some weight. Short episodes of low fever recurred at long intervals accompanied by slight anal bleeding. He was admitted to the Veterans Administration Hospital for the third time for a week in April, 1951. The results of study were meager. The sedimentation rate was 38 mm. per hour, and the lymph nodes were palpable. One from the inguinal region was excised and showed no significant changes. Roentgenograms of the hands, wrists, elbows, knees, and spine were normal.

Improvement continued, and his weight increased to 79 kg. (174 lb.). He felt well by September, 1951, two years after the onset of illness, and worked without discomfort. During this time there were transient bouts of diarrhea. He noticed that his mouth was becoming progressively drier. In February, 1952, he was examined once by Naval physicians and again for fitness for foreign service. No abnormalities were found. In March burning on urination led to cystoscopy, but nothing of significance was seen.

On arrival in Beirut in April, 1952, the patient noticed three lentil-sized subcutaneous nodules on the shaft of the penis. Burning on urination continued, and erection was painful. A nodule was seen in the urethra during cystoscopy. There was a raised round erythematous plaque 1.5 cm. in diameter on the dorsum of the right hand. The plaque and the nodules disappeared in three or four weeks. The temperature was normal during three days of study in the hospital. The blood count, urinalysis, and blood protein were normal. The patient weighed 70.8 kg. (156 lb.). There were no significant symptoms except transient bouts of diarrhea. Numbness had been noticed at times along the lateral side of the left thigh for several months.

During the summer the patient occasionally raised a small amount of brownish or bright red blood mixed with saliva which came from "sores" in his mouth. Small amounts of blood were blown from his nose. His conjunctivas at times were red and edematous. Dryness of his mouth required water added to food for deglutition. He began to tire easily and felt weak and stiff. He was readmitted to the hospital for study under our observation in November, 1952.

He was thin and pale. There were discrete punctate purpuric spots in the buccal and pharyngeal mucous membrane, nasal septum, turbinates, and conjunctivas. Several "blood blisters" were on the tongue and gums. The vesicles ruptured, discharged bloody fluid, and left shallow aphthous-like ulcers. The liver was enlarged and firm and extended 3 or 4 cm. below the costal margin. The hemoglobin measured 11 gm.; the red cells numbered 3,700,000, and the leucocytes, 4,000, of which the polymorphonuclear cells composed 53%, lymphocytes 30%, mononuclear cells 2%, and eosinophiles 15%. The platelets numbered 150,000; the bleeding time was 2.5 minutes; coagulation time, 6 minutes; clot retraction, 2 hours, and prothrombin time, 13.5 minutes. The bilirubin measured 0.6 mg. total and 0.15 mg. direct-reacting. Total proteins of the blood were 7 gm.; albumin 4 gm. and globulin 3 gm. Serologic tests for syphilis gave negative results. Urine showed faint albuminuria, with a few hyaline casts. The temperature ranged between 37 C. (98.6 F.) and 37.5 C. (99.5 F.); pulse rate was 90 to 110. Blood pressure was 120/70.

The patient gradually lost weight and strength and was studied on several more occasions in the hospital. In January, 1953, weakness was the chief complaint and slight bleeding from the nose, mouth, and anus was occasionally noted. His mouth was dry; he walked stiffly, was listless, was dyspneic on exertion, and had been sexually impotent for several months. There were "blood blisters" on his tongue and yellowish plaques on the mucous membrane of the lower lip; the conjunctivas were severely injected; there were three red papules on the right cheek, and a lentil-sized subcutaneous nodule appeared in front of the right ear. The liver increased further in size. The spleen was not palpable but was seen to be enlarged in a roentgenogram. Roentgenography showed no abnormalities in the heart, lung, kidneys, or bones. The temperature occasionally rose to 37.5 C. (99.5 F.); the pulse rate was continuously over 90 per minute, often 100 or 120. There was a plaque of erythema on the dorsum of the right wrist about 2 cm. in diameter, similar to the one which had been present nearby in April. The results of laboratory studies were similar to those found before; the leucocytes numbered 4,000 in several counts. Marrow from the sternum showed no abnormality. Sigmoidoscopy revealed a few internal hemorrhoids and a mildly congested mucosa without ulcers or erosion. A cuff test applied to the arm caused no petechiae. An electrocardiogram showed normal rate tachycardia; T diphasic in Leads II and V_2 was believed to be indicative of myocardial change. The bilirubin measured 0.7 mg. total and 0.2 mg. direct-reacting; sulfobromophthalein (Bromsulphalein) test, 14% retention; cephalin flocculation, negative. Primary amyloidosis was suspected, and tissue for biopsy was taken successively from the liver by needle aspiration, from a plaque on the inner surface of the lower lip, from the plaque on the hand, at random from the normal-appearing rectal mucosa, and from apparently normal vastus intermedius muscle.

The patient was sent to a hospital in the United States in February, 1953, where he died after several weeks and necropsy was performed. While he was at that hospital the only significant results of laboratory tests showed the following: Erythrocytes between 1,500,000 and 3,000,000; leucopenia (2,000 to 4,000 cells); a sedimentation rate of 38 mm. per hour; no Bence-Jones proteinuria; calcium, 11.5 mg.; phosphorus, 3 mg.; acid phosphatase, 8.2 mg.; alkaline phosphatase, 13 mg.; Congo red, 49% retained; sulfobromophthalein test, 41% retention; serum bilirubin, 0.92 mg., and aspirated bone marrow contained some trinucleated cells. A roentgenographic bone survey showed no abnormalities.

Report of Biopsies

Excised specimens from the oral and rectal mucosa, a dermal plaque, and skeletal muscle and a portion of liver obtained by needle biopsy were fixed in 10% aqueous solution of formalin. Paraffin sections were stained with hematoxylin and eosin, toluidine blue, Congo red, Van Gieson's stain, Schiff's periodic acid stain, and Wilder's silver stain and methyl violet.

Liver.—Amyloid appears as a thin homogeneous granular layer between the endothelium of the sinusoids and the hepatic cells. The hepatic cells are not compressed (Fig. 1).

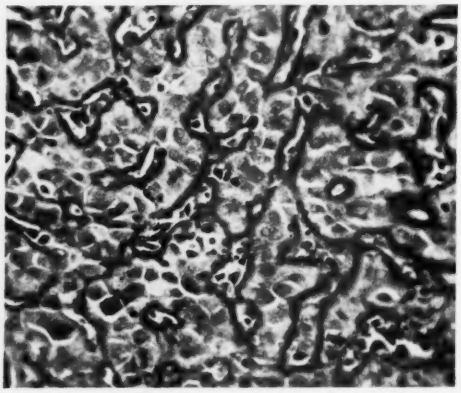

Fig. 1.—Amyloid is present in thin homogeneous layers between the endothelium of the sinusoids and the hepatic cells. The cells are not compressed. Periodic acid-Schiff stain. (Figures 1 to 5 are from biopsy specimens.)

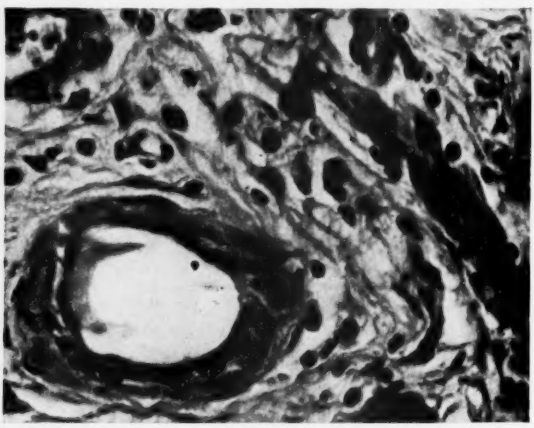

Fig. 2.—Oral mucosa. Amyloid surrounds the duct of a mucous gland. It surrounds and strangulates a capillary shown in longitudinal section. Periodic acid-Schiff stain.

Oral Mucosa.—Amyloid is present around some of the ducts of the mucous glands, capillaries, and arterioles. In the ducts it forms a zone around the epithelial lining. In the blood vessels it is irregularly distributed, and it is limited in the capillaries to the so-called pericapillary sheath of Zweifach. Some of the capillaries are surrounded and strangulated. In the arterioles, it is deposited externally to the endothelium in the perivascular adventitial tissue, including the media, and obliterates the smooth muscle fibers. Some arterioles are partially encircled, others completely (Fig. 2).

Rectal Mucosa.—Amyloid is distributed in the blood vessels in a manner similar to that in the oral mucosa.

Dermal Plaque.—Besides the characteristic vascular deposition there is interrupted linear deposition in the region of the basement membrane between the dermis and the epidermis (Fig. 3).

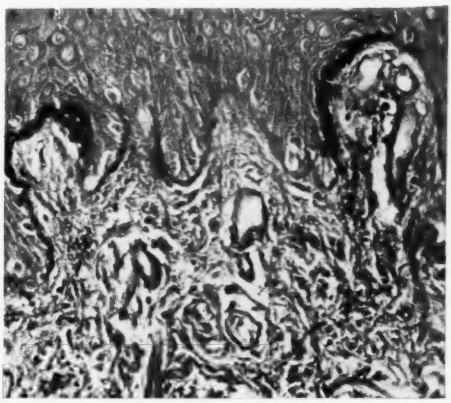

Fig. 3.—Dermal plaque. Amyloid in interrupted linear deposits between the dermis and epidermis. Periodic acid-Schiff stain.

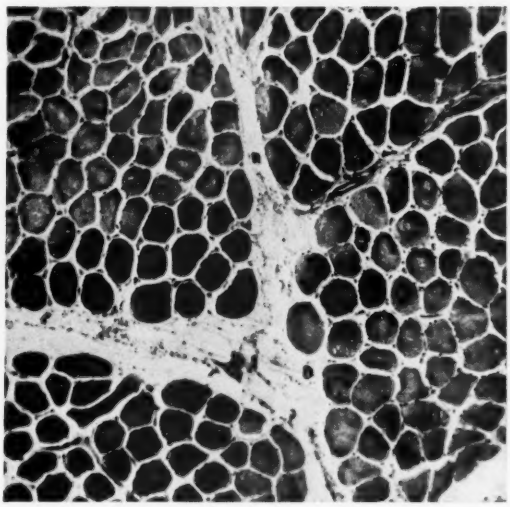

Fig. 4.—Groups of involved muscle fibers and isolated ones among normal fibers. The darker fibers are deeply stained with Congo red. They are not to be confused with normal dark fibers.[84]

Muscle.—No amyloid is seen in the connective tissue stroma between muscle fibers, as in other reported cases, except in some of the arterioles and capillaries, where it is the same as in other tissue. Instead, amyloid, or a substance resembling amyloid, is present within muscle cells. As shown in Figure 4, patchy groups of involved fibers are scattered among normal ones. Fibers

are transformed into pockets, some filled and others partly filled with a substance which behaves histochemically toward certain stains as amyloid does elsewhere. The amount of substance varies in different parts of the same fiber (Fig. 5). Where it is most intense, the fiber is swollen and the myofibrils are obliterated. In others, on cross section, concentric rings are formed within cells, with myofibrils in the center or pushed to the side. Unfortunately there is no stain specific for amyloid, but there is reason to identify the substance in striated muscle cells as amyloid. It reacts histochemically like the amyloid in adjacent capillaries and elsewhere, and clinical evidence of involvement of muscle had been present, as in the case of Iverson and Morrison.[14]

Report of Necropsy

A summary of observations at necropsy made elsewhere was received. The heart weighed 490 gm. The myocardium was brown, and the left ventricular wall was mottled brown and tan. The lungs showed evidence of chronic passive congestion and areas of hemorrhage. The lymph nodes of the neck, axillas, mediastinum, periaortic region, pancreas, and pelvis were large, soft

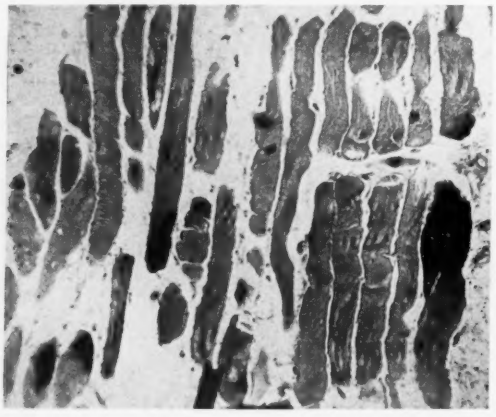

Fig. 5.—Striated muscle. Substance deeply stained with Congo red is distributed irregularly in certain fibers. Where deposition is most intense, the caliber of the fiber is increased and the myofibrils are obliterated.

or rubbery, pinkish-gray, and homogeneously light tan with small red areas on section. The liver weighed 4,730 gm.; the spleen, 700 gm. The pancreas was of firmer consistency than usual. No abnormalities were seen in the gastrointestinal tract, pelvic organs, skeletal system, or bone marrow.

Stained sections of organs and tissues were sent to us for study. None was available for special staining. In our interpretation, the following changes were noted.

Kidney.—Longitudinal streaks of lymphocytic infiltration and tubular damage suggestive of chronic pyelonephritis extend from the cortex to the medulla. Scattered throughout the cortex are a few balls of hyalinized fibrosis, probably hyalinized glomeruli. A homogeneous finely granular eosinophilic substance (amyloid?) is found in the walls of the arterioles, glomeruli, tubules, and interstitial connective tissue. The walls of the blood vessels are extensively involved but the lumens are not occluded. The glomeruli show extensive deposits in the afferent and efferent vessels (Fig. 6), but the capillary tufts rarely are affected. Finely granular eosinophilic masses are seen on the lining of Bowman's capsules throughout the section. Similar masses are present in the lumens of the convoluted tubules and in the epithelial cells of the ascending and descending limbs of Henle's loops. Where the intracellular deposit is intense the substance

encircles the lumen; where it is mild it is present between the basement membrane and the nuclei (Fig. 7). In such areas the stroma is free from amyloid. The interstitial connective tissue shows irregular areas of deposit.

Liver.—There is extensive atrophy of the hepatic cells due to large amounts of amyloid in the walls of the sinusoids. In the portal triads there is amyloid in the walls of the hepatic artery and portal vein, but the bile ducts are normal. Minute amounts of amyloid are in the central veins.

Spleen.—Amyloid replaces the Malphigian corpuscles and is present in the central arterioles. There is uniform amyloid deposit in the walls of the sinusoids of the pulp.

Marrow.—There are scattered masses of amyloid and uniform distribution of megakaryocytes. In three stained sections of marrow, there is an increased number of cells with eccentric nuclei resembling plasma cells scattered among the hemopoietic elements. Sections for differential staining were not available.

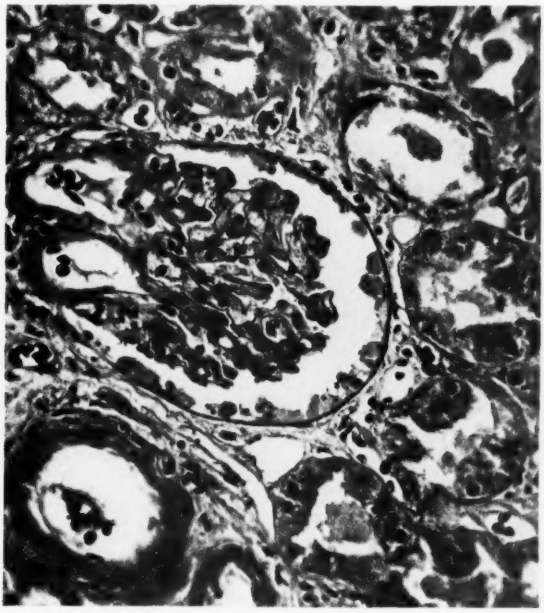

Fig. 6.—Amyloid in the walls of afferent and efferent vessels and none in the capillary tuft of a glomerulus. Inside Bowman's capsule are acidophilic granular bodies 8 to 12 μ in diameter characteristic of amyloid. Amyloid in the wall of an adjacent arteriole. (Necropsy specimen.)

Lymph Node.—The stroma and blood vessel walls contain abundant amyloid or acidophilic granular material. In the germinal centers it is intracellular. A few multinucleated giant cells are present in some of the extensively involved follicles. Amyloid is within some of the macrophages. There are a few tubercle-like old foci.

Heart.—The myocardium shows atrophic and degenerative changes. Amyloid is in the blood vessel walls and interstitial tissue. In some of the muscle cells amyloid seems to invade the fibers from the periphery. Amyloid is present around the arterioles.

Tongue.—There is vacuolization of the squamous epithelium and amyloid is in the basement membrane and walls of superficial vessels. Amyloid is in the connective tissue of the superficial bundles of muscle and is inside some of the muscle fibers.

Skeletal Muscle.—The capillaries and arterioles show irregular distribution of amyloid, while the connective tissue stroma is free. The sarcolemma of some muscle fibers is an empty envelope; in others it contains a homogeneous finely granular faintly staining eosinophilic substance (amyloid?). In these areas the muscle nuclei are pyknotic and clumped together. In some fibers the intracellular granular substance is continuous with visible striations. The fibers which have visible striations are of two kinds. Some are pale, uniform, and wavy and have normal striation throughout. The others are darker and irregular in size, with irregular striations. They may be continuous with empty sarcolemma or with faintly staining granular nonstriated substance.

Lung.—There are passive congestion and mild organizing pneumonia and patches of lipoid pneumonia. Amyloid is in some of the pulmonary arterioles.

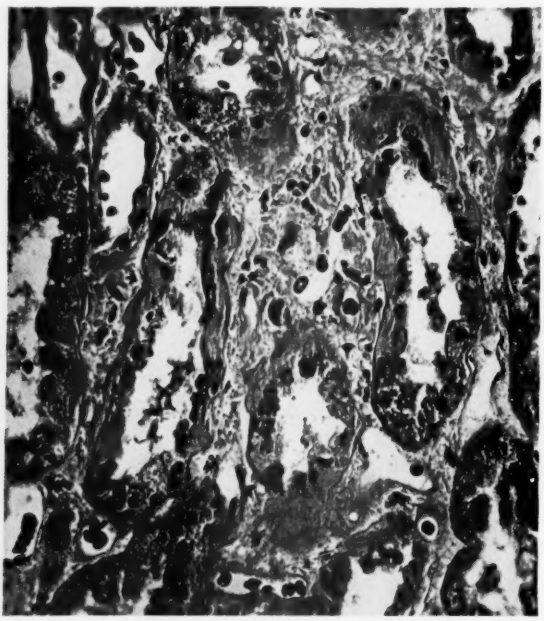

Fig. 7.—Amyloid between the basement membrane and nuclei of epithelial cells of Henle's loops, in oblique section. The nuclei have not degenerated, and no amyloid is between the nuclei and the lumen nor in the stroma between the tubules. (Necropsy specimen.)

Pancreas.—There are congestion and petechial hemorrhages. Amyloid is present in the arterioles, capillaries, and connective tissue septums.

Thyroid.—Many arterioles and capillaries contain amyloid. Many acini contain little or no colloid, and the colloid seems of thin consistency.

Parathyroid.—There is extensive replacement of the connective tissue stroma and involvement of blood vessels with amyloid.

Adrenal.—The cortex is almost replaced by amyloid; only a few subcapsular cortical cells are intact. The medulla is minimally involved. Amyloid is present in the arterioles and capillaries of the surrounding adipose tissue.

Sections of the urinary bladder, prostate gland, and testicles were not received for study. According to report, amyloid is present in the blood vessels of each, in the fibromuscular stroma

of the prostate, and in the basement membrane of the tubules of the testicle. The brain and pituitary were normal. No mention was made of the intestinal tract, except for congestion of the gastric mucosal vessels.

SUMMARY OF CASE

The patient had an undiagnosed intermittent ailment for two years, from 1949 to 1951. There were stiffness, soreness and aching of muscles and joints, febrile episodes, transient lymphadenopathy, occasional bleeding from the nose and anus, weakness, and loss of weight. All studies and laboratory tests failed to reveal the cause. He improved, regained some weight, and seemed to be in good health for about eight months except for transient bouts of diarrhea and numbness of the left thigh. Persistent xerostomia began. Transient nodules appeared on the penis and in the skin and urethra.

New signs and symptoms in addition to stiffness began in April, 1952. There were punctate purpuric spots and "blood blisters" in the oral mucous membrane, conjunctivitis, local dermal eruptions, sexual impotence, insomnia, asthenia, pallor, hepatomegaly, anemia, leucopenia, and progressive loss of weight. Amyloidosis was suspected and was proved by biopsy. Amyloid was found in the oral mucous membrane, skin, and liver and in tissue from areas selected at random from apparently normal rectal mucosa and muscle. The transient penile and dermal papules most likely were of amyloid.

The nature of the illness observed elsewhere between 1949 and 1951 is uncertain. It may have been one which led to secondary amyloidosis, an unrelated one, or, most likely, primary amyloidosis. If the latter is correct, the diagnosis is primary amyloidosis clinically evident for nearly four years. Except for the febrile episodes, the signs and symptoms described conform generally to the tabulation of leading features of 71 described cases of primary amyloidosis.[5] Stiffness of muscles and joints and bleeding from the mucous membrane of the mouth, nose, and rectum may be accounted for by amyloid deposits in the early period of the illness. Muscular stiffness, in one case lasting 14 years, has been observed by others.[15] Xerostomia probably was caused by amyloid involvement of the mucous glands and ducts. Examples of xerostomia, lymphadenopathy, and numbness in amyloidosis are cited by Goltz.[16] Impotence also has been recorded,[17] but whether, in our case, it was caused by neural or by gonadal involvement, as seen at necropsy, is uncertain. Macroglossia and cardiac failure were not present, but the electrocardiographic changes and tachycardia suggested the presence of amyloid in the myocardium, and this was observed histologically after death. Amyloid was present in almost all the tissues examined and in large amounts in the liver, spleen, and parathyroid and adrenal glands. A diagnosis of multiple myeloma and secondary amyloidosis was made by those who performed the necropsy at another hospital, because of the presence of plasma cells in marrow.

The case illustrates the difficulty in classification. It is apparently one of primary amyloidosis, yet the gastrointestinal tract, heart, and lungs were not greatly involved and the tongue was not enlarged; the liver and spleen were laden with amyloid as is characteristic of secondary amyloidosis, and an increased number of plasma cells in the marrow raised the question of myeloma and secondary amyloid disease.

RELATION OF PRIMARY AND SECONDARY AMYLOIDOSIS

Primary and secondary amyloidosis have more in common than is generally believed. Although the heart, gastrointestinal tract, lungs, and muscle are more prominently involved in the primary form and the kidneys, spleen, and liver in the secondary form, amyloid is distributed widely in similar places in both. Both may be systematized, or generalized, since amyloid is deposited in the vascular system, around capillaries, in the muscularis of arteries, in fibrous tissue, and in striated muscle. The sites of deposition, as found after death in small series of cases of primary and secondary amyloidosis, are shown in the accompanying Table of Thingstad's [5] and Dahlin's [18] figures of incidence. With few exceptions, the statistical differences are not great. The skin and mucous membrane often are involved in primary amyloidosis but also are in the secondary form, the incidence of which is not shown in the Table. The skin was affected in 7 of 14 of

Organs and Tissues Involved in Primary and Secondary Amyloidosis at Necropsy

	Amyloid Involvement, % of Cases		
	Primary Amyloidosis (Thingstad; 54 Cases)	Primary Amyloidosis (Dahlin; 8 Cases)	Secondary Amyloidosis (Dahlin; 30 Cases)
Heart	85	100	43
Gastrointestinal tract	61	100	55
Tongue	44	...	..
Liver	39	62	87
Kidney	39	75	93
Spleen	37	100	100
Striped muscle	35	71	0
Thyroid	24	88	59
Skin	25	...	..
Lymph nodes	17	62	68
Adrenal	..	72	93
Pancreas	..	75	63
Prostate	..	68	62
Lung	..	89	10

Schilder's tuberculous patients.[19] Random biopsy of normal-appearing gingival tissue showed amyloid in 14 of 47 other patients with amyloidosis secondary to tuberculosis.[20] It is likely that the recorded differences in sites of deposition would become even less if amyloid were sought more carefully in unsuspected places. It would seem, therefore, that the important difference between primary and secondary amyloidosis is a clinical one and depends on the presence or absence of a preceding causative disease.

Mode of Origin.—Involvement of mesenchymal tissue and distribution of amyloid in the classified kinds of amyloidosis suggests common factors in its origin. A macromolecular protein substance, apparently of cellular origin, is formed and held locally or circulates in the blood and deposits as amyloid around capillaries in smooth muscle, around the endothelial lining of blood vessels, in the reticulum and sinusoids of parenchymatous organs, and on and around the cells of involved organs. Presumably, after some change or abnormality in vascular permeability and/or in the intercellular ground substance, normal or abnormal protein escapes into the intercellular spaces and stays there. Because it is rela-

tively inert, it is degraded slowly and accumulates more rapidly than it is removed. The accretions then push between muscle fibers and between cells of parenchymatous organs and obliterate them.

If the primary form arises from some inherent defect, perversion, or injury of mesenchymal tissue, normal or abnormal protein may enter, settle, and accumulate there.[1] The process may be so slow that years elapse before masses of substance called amyloid grow large enough to obliterate vessels and cells and cause clinical disturbance. Only occasionally may large amounts collect in the spleen, liver, and kidneys, whose function it is to remove certain substances from the blood. Evidence in support of this view is provided by the presence of amyloid in the hearts of extremely old persons,[21] and in senile mice, in which the incidence of amyloidosis increases with age.[3] The existence of some inherent defect is suggested by recent recognition of the hereditary nature of amyloidosis in some strains of mice[3] and in a few family groups.[21a]

Localized, or tumor-forming, amyloidosis may result from the formation and/or accretion of the substance in local areas of abnormal mesenchymal or other tissue. The distribution of amyloid in multiple myeloma might be explained by its slow deposition during the existence of plasmacytoma, beginning long before the latter comes to clinical attention.

Amyloidosis does not develop in all victims of chronic disease and hyperglobulinemia nor in all animals injected experimentally with various substances to cause amyloid. It is possible that, in spite of hyperglobulinemia, amyloidosis does not occur unless, as presumed in the primary form, mesenchymal tissue also is defective or is injured by the preceding disease. In that case, because of its rapid formation and excessive amount, much of the normal or abnormal circulating protein may settle in mesenchymal tissue and elsewhere and accumulate as amyloid more quickly than in the primary form. If this combination of circumstances occurs, the spleen, liver, and kidneys have to deal with amounts of retained protein with which they are unable to cope and the substance piles up, so to speak, as inert macromolecular protein, or amyloid. The regular tinctorial characteristics of rapidly forming amyloid of the secondary form may be explained by its youth and homogeneity; the characteristic metachromasia in the slowly developing primary form may be due to changes incident to variation in age or composition.

There is controversy as to whether amyloid is formed and collects locally in tissue or is deposited from circulating protein. Both may take place. As cited by Goltz,[16] a number of observers noted amyloid within myeloma-plasma cells, as if it were formed there, since plasma cells ordinarily are not phagocytic. This mode of origin is in line with older views on the cellular formation of other blood proteins.[22] Amyloid noted in polymorphonuclear cells and macrophages may be accounted for by phagocytosis.[23]

Amyloid in muscle cells as noted in the case described here does not appear to have been synthetized locally nor to be a product of degeneration. Nor does it appear to have entered the cells by invasion or invagination, as has been suggested by others.‡ Partial strangulation of nutrient capillaries by amyloid may have resulted in an alteration of the cells they supplied and permitted imbibition of amyloid through the sarcolemma. Retention of the substance and its gradual

‡ References 8, 15, and 24.

accumulation between the myofibrils caused their obliteration. If the substance seen in epithelial cells of renal tubules is amyloid, it may have been resorbed as a protein from the urine or may have come from the blood supply.

RELATION OF AMYLOID TO MYELOMA (PLASMACYTOMA)

It is probable that, if more careful search were made, amyloid would be found in more than the estimated 15 to 25% of cases of multiple myeloma in which it has been reported.§ It is unlikely, however, that myeloma precedes all cases of "primary" amyloidosis, as suggested by Apitz.‖

In the case described here, multiple myeloma was diagnosed by others on the sole basis of an increased number of plasma cells in the marrow at necropsy. There was no other evidence of myeloma. Bence-Jones protein was not found in the urine, the blood proteins were normal, rouleaux did not form, the bones showed no roentgenographic changes, and no tumors were present after an illness lasting four years. No abnormal cells were seen in the sternal marrow examined on four occasions during life nor elsewhere after death.

Similar diagnostic uncertainty confronted other observers in whose cases of supposed primary amyloidosis a few plasma cells were seen in the marrow at biopsy or necropsy.¶ In the absence of all other evidence of myeloma it is doubtful if such a diagnosis is justified. Mature plasma cells may compose from 10% [30] to 25% [31] of cells in the marrow during chronic tuberculosis, syphilis, and neoplastic disease. It seems more reasonable to recognize a state of plasmacytosis. It is possible that a long-standing increase in the number of scattered plasma cells, not necessarily plasmacytoma, may give rise to amyloidosis or that the presence of amyloid may induce a plasmacytic response.

Amyloidosis as a form of proteinosis may be compared with other so-called storage or retention diseases associated with excessive amounts of various normal or abnormal substances and their deposition and accretion. In glycogenosis (von Gierke's disease) there are excessive deposits of glycogen in myocardial muscle fibers, in the muscles of the walls of blood vessels, and elsewhere. A derangement of lipid metabolism and cholesterolemia apparently results in the deposition of atheromatous plaques in abnormal blood vessels.[32] In other lipoidoses (Gaucher's and Niemann-Pick's diseases) deposits are found intracellularly in the reticuloendothelial system and elsewhere. They are caused either by overproduction or underexcretion or by abnormal synthesis, transport, or catabolism of different substances and may be regarded as macromolecular symptom complexes of endogenous origin.[33] There is controversy about these as well as to whether the substances are deposited or are synthesized locally.

SUMMARY

A case of amyloidosis is reported which we regard as of the primary type. Although an increased number of plasma cells were in the marrow, no other evidence of plasmacytoma was evident. Amyloid was present in tissue removed at

§ References 25 and 26.

‖ References 27 and 28.

¶ References 18 and 29.

biopsy from the liver, skin, oral and rectal mucosa, and muscle and at necropsy in most of the tissues and organs examined. Amyloid was present inside of muscle and epithelial cells and in macrophages.

From studies in many reported cases it would seem that primary and secondary amyloidosis have much in common. Mesenchymal tissue and parenchymatous organs are affected in both, and both may be systematized. A hereditary factor may be implicated. The primary form is distinguished chiefly by the absence of a discernible cause; by the predominant involvement of the heart, gastrointestinal tract, lung, and muscle, and by its slow progression. The more rapid development of secondary amyloidosis and the predominant involvement of the spleen, liver, and kidneys may be caused by a defect in mesenchymal tissue in combination with hyperproteinemia incident to a preceding disease. Amyloidosis, regarded as a form of proteinosis, has certain features in common with other retention or storage diseases, such as glycogenosis and lipoidosis.

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FATAL CARDIAC FAILURE IN PERSONS WITH THORACIC DEFORMITIES

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THE FUNCTIONAL disturbances of the circulation and of respiration which are, at times, associated with kyphoscoliosis have not received the attention they deserve, in spite of the fact that they have been studied by many authors. Deformities of the thorax are usually classified as lordosis, kyphosis, kyphoscoliosis, pectus excavatum, and pectus carinatum. Of these, kyphosis, kyphoscoliosis, and pectus excavatum are the chief offenders. Lordosis usually presents no symptoms.

Hippocrates [1] recognized that dyspnea is a common finding in these patients. The first descriptions of early death in persons suffering from kyphoscoliosis did not incriminate the cardiovascular system, and it was not until the end of the last century that continental observers described heart failure as being the commonest cause. Finley,[2] in 1921, remarked on the almost complete absence in English literature of any reference to the effects of scoliosis on the thoracic viscera, and he presented four such cases, in which the patients died with signs of heart failure. It would seem that the association of cardiac hypertrophy and dilatation with thoracic deformity has been largely ignored in English medical literature. In our review of the available literature before this date it is interesting to find a reference to this condition in a series of lectures by Dr. P. M. Latham,* at St. Bartholomew's Hospital in London, in 1847.

This was the first good description of this entity and so deserves quotation here:

> Strange things happen to the heart when the chest is deformed. Its sounds and impulses and resonance, be they what they may, are now worth nothing at all as guides to diagnosis. The heart is dragged from its proper seat and imprisoned in some strange place and perhaps turned almost topsy-turvy by the encroachment of the vertebral column and the approximation of the ribs. And thus cramped in and hooped about with bone at every movement it gives a jar that may be felt and a sound that may be heard in every part of the chest. And this sound which is thus conveyed at a distance is seldom the natural sound; but a loud whiz, the same in kind and loudest in degree which belongs to mechanical impediment from valvular disease. And mechanical impediment there is, but valvular disease there is none. The encroachment cannot be without mechanical impediment and this impediment cannot be without hurt and hindrance first to the functions and then to the structure of such organs as the heart and lungs.

Coombs [5] in 1930 reported fatal cardiac failure occurring in persons with angular deformity of the chest, which was the first report from England. In the United

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* References 3 and 4.

States a single such case was reported by Reid [6] in 1933. In contrast, numerous clinical notes are found in the French and German literature. Constantin Paul [7] in 1883 included in his textbook an entire chapter entitled, "Le Coeur de Bossus."

Romberg [8] was of the opinion that persons with high-grade kyphoscoliosis nearly always die of heart failure, although he felt that pulmonocardiac failure is rare, in that it is limited to those with severe chest deformities. We are in agreement with this view, though Chapman [9] believed it was of common occurrence in those deformed. The incidence of chest deformity is unquestionably high, but it is difficult to estimate the number of those who suffer pulmonocardiac failure. It would seem doubtful that moderate kyphoscoliosis or pectus excavatum ever causes harmful intrathoracic changes. However, it would appear obvious that severe kyphosis or scoliosis, either of which usually becomes kyphoscoliosis, often causes changes in the thoracic viscera sufficient to produce the symptoms and signs of pulmonocardiac failure.

The etiology of the thoracic deformity is not always clear. Although poliomyelitis was unrecognized as such in the earlier reports, it is possible that it always has been the chief cause of thoracic deformities. Congenital or hereditary defects, rickets, trauma, and tuberculosis have been other etiological factors. The incidence of some degree of scoliosis following poliomyelitis has been variously reported at 5 to 30%. Severe chest deformities, while occurring in both sexes, seem to occur more frequently in the male. All five cases in Kerwin's [10] report were in males. For some unknown reason right-sided kyphoscoliosis is more frequent than left-sided (110 of 126 cases of Chapman's [9] entire review of the literature). In general, patients suffering from "hunchback" seldom attain old age. The average age at death is about 30 years. In Kerwin's [10] report only one died young, and this does not substantiate the claim made by some that these patients rarely pass the age of 40.

Pulmonocardiac failure as a result of severe deformity of the thoracic cage is not often seen in routine autopsies. In Kerwin's [10] series it was present on an average of only once in 1,340 cases, or approximately 0.075%. Finley,[2] on the other hand, indicates that the condition cannot be very uncommon, since three of his four cases occurred within one year. Our interest was focused on this syndrome when a young male patient (Case 5, W. D.) entered Cook County Hospital in acute right heart failure, which led to differential diagnoses of rheumatic heart disease, congenital heart disease, and pulmonocardiac failure. Postmortem examination confirmed the diagnosis of pulmonocardiac failure. In reviewing all the autopsies performed at the Cook County Hospital from 1929 to July 1, 1953, we could find only 11 cases, out of a total of 30,729 necropsies, in which the cause of death could be attributed to pulmonocardiac failure. This is once in 2,730 autopsies, or 0.036%, statistically, then, a rare syndrome. The pathological data of these cases are shown in the Table, and the clinical course and postmortem observations of five cases are here reported.

CASE 1.—J. J., a 55-year-old white man, entered Cook County Hospital Jan. 23, 1935, as an emergency case. He was admitted to the medical service very dyspneic and unable to give a comprehensive history. He informed the examining physician that he had had the chest deformity all his life, which he believed was the cause for his always being short of breath. Three months before admission there was a gradual onset of swelling of the ankles, legs, and genitalia. Associated with this was an increase in the patient's dyspnea, so much, in fact, that he thought he had better enter the hospital.

On examination, patient was a markedly deformed, poorly nourished white man, intensely dyspneic. His blood pressure was 128/94, respirations 40 per minute, pulse rate 112 and

regular, and temperature 97.6 F. orally. There was marked kyphosis of the thoracic spine. His chest was hyperresonant to percussion in the upper one-third, with fine crackling rales in both lower lung fields. The heart borders and apex were difficult to determine; however, a Grade 2 apical systolic murmur was present. In the abdomen there was some tenderness to deep palpation in the right lower quadrant. There was marked pitting edema of both lower extremities, the penis, and the scrotum. The clinical impression was cor pulmonale with myocardial failure. The patient was given digitalis, 1 gm., and morphine sulfate, ¼ grain (15 mg.), immediately. The dyspnea continued, and at 8:00 a.m. the next morning oxygen therapy was started and morphine sulfate, ¼ grain, and atropine sulfate, 1/120 grain (0.5 mg.), were given subcutaneously and were to be repeated every six hours for three doses if the patient was still markedly dyspneic. The patient died at 1:05 p. m. Jan. 24.

Autopsy.—The body was that of an elderly white man with cyanotic lips, face, fingernails, and buccal and oral mucosa. The pupils were round and equal. The anterior portion of the chest bulged forward; the anterior-posterior diameter of the chest was 30 cm., and the transverse

Pulmonocardiac Failure

Patient	Age, Yr.	Sex	Skeletal Deformity	Cause of Lesion	Heart Weight, Gm.	Dilation of Heart	Rt. Ven. Thickness, Mm.	Secondary Lung Pathology	Pulmonary Atherosclerosis
S. F.	45	F	Lt. kyphoscoliosis	Unknown	350	Rt. Aur. Rt. Ven.	6	Bronchiectasis	++
B. D.	60	M	Lt. kyphoscoliosis	Injury at 18 mo.	305	Rt. Aur. Rt. Ven.	6	Emphysema, bronchopn., atelectasis	++
M. O'C.	41	M	Rt. kyphoscoliosis	Tuberculosis	280	None	5	Atelectasis	0
M. S.	65	M	Kyphosis	Unknown	440	Rt. Aur. Rt. Ven.	6	Bronchiectasis	++
J. J.	55	M	Kyphosis	Unknown	410	Rt. Ven.	10	Atelectasis	+++
A. T.	31	M	Kyphosis, scoliosis, pectus carinatum	Injury at 1 yr.	460	All chambers	7	Atelectasis, bronchiectasis	0
M. J.	44	F	Rt. kyphoscoliosis	Unknown	300	Rt. Aur. Rt. Ven.	10	Chronic passive congestion	0
C. N.	76	M	Pectus carinatum	Unknown	200	Rt. Aur. Rt. Ven.	4	Bronchiectasis	0
G. D.	54	M	Rt. scoliosis	Injury	440	Lt. Ven. Rt. Aur. Rt. Ven.	5	Emphysema	++
E. L.	38	F	Rt. kyphoscoliosis	Unknown	350	All chambers	6	Bronchopn., passive congestion, atelectasis	+
W. D.	31	M	Rt. kyphoscoliosis, pectus carinatum	Unknown	600	All chambers	12	Emphysema	+++

diameter was 25 cm. The abdomen was distended 2 cm. above the level of the chest. The penis, scrotum, and lower extremities were very edematous. There was a marked kyphotic deformity of the lower dorsal and upper lumbar spine. The heart weighed 410 gm. The left ventricle was 15 mm. in thickness, and the right ventricle, markedly thickened, 10 mm. The myocardium was dark red-brown and moderately soft. The valves and coronary vessels were normal. In the chest, the right pleural cavity was completely obliterated by firm fibrous adhesions. In the left pleural cavity there were diffuse adhesions about the lateral and posterior aspects of both lobes. The pleural cavities were much reduced in volume, the diaphragm on the left being only 7 cm. from the apex and the lung on the right side only 6 cm. from the apex. Both lungs were small; the right lung measured 15 by 7 by 5 cm., and the left lung, 15 by 8 by 5 cm.; the combined weight was 570 gm.; they were crepitant throughout and on cut section pinkish-gray and dry. In two of the smaller branches of the left pulmonary artery there were a few fatty plaques up to 5 mm. in diameter. The abdominal cavity contained 1 liter of cloudy yellow fluid. The liver weighed 900 gm. and was small and firm. Its cut surface was yellow-brown, with distinct acinar markings.

Microscopic Examination.—Except for slight passive congestion noted on sectioning in the liver and kidneys, the examination was limited to the findings in the lungs. Here the alveolar septa were thin-walled, except in an occasional area where the septal capillaries were dilated and filled with blood. In one area a small branch of the pulmonary artery was completely occluded by a thrombus in which there was partial organization. The arterioles throughout the entire section were thickened.

Diagnosis.—The chief anatomic diagnoses were kyphosis of the thoracolumbar vertebrae, with reduction in volume of the pleural cavities; moderate eccentric hypertrophy of the heart, especially the right ventricle; chronic passive congestion of the liver, spleen, and kidneys; very slight atherosclerosis of the smaller branches of the pulmonary artery; fibrous obliteration of the right pleural cavity and partial fibrous obliteration of the left pleural cavity, and abdominal ascites.

CASE 2.—A. T., a 31-year-old white man, entered the Cook County Hospital on Feb. 27, 1941, as a cardiac emergency. A history was unobtainable, because of the patient's critical condition, other than that he had shortness of breath for two days and a vague tightness in his throat for three weeks, with some cough productive of white sputum. The patient had injured his back when he fell off a porch at one year of age and had been treated for pneumonia at the Cook County Hospital in 1939.

The physical examination revealed an extremely dyspneic cyanotic fairly well-nourished white man with a marked anterior deformity of the sternum, thoracic kyphosis, and lumbar lordosis. The neck veins were distended. The apex beat of the heart was not discernible and its borders could not be made out because of the chest deformity. A soft systolic murmur was heard over the entire precordium. The pulse rate was 164 and regular, and the blood pressure was 130/90, with respirations of 34 per minute. The breath sounds were vesicular throughout, and there were scattered moist rales heard in the anterior chest. The abdomen was protuberant; there was no evidence of ascites, and there was a 2+ pitting edema. Laboratory examination revealed a normal urine, a negative blood Kahn test, and an ECG interpretation of sinus tachycardia with a normal axis deviation. The nonprotein nitrogen was 50 mg., creatinine 1.4 mg., and blood chloride 455 mg. per 100 cc.

The clinical diagnosis was acute cardiac failure. The patient was given intravenous digitalis, intranasal oxygen, and morphine sulfate, ¼ grain (15 mg.), and atropine sulfate, 1/100 grain (0.6 mg.), intramuscularly. The patient became more dyspneic and cyanotic and died 4 hours 10 minutes after admission.

Autopsy.—The body was that of a moderately well-developed well-nourished white man with a cyanotic discoloration of the face, neck, and ears. The finger nails and toenails were also of a cyanotic hue. The chest revealed marked dorsal kyphosis, with some right scoliosis and anterior convexity. The sternum extended forward 12 cm. from the sternoclavicular junction, forming a dome-like projection, which was 15 cm. at its base. The abdomen was at the level of the xiphoid process. Moderate pitting edema of the ankles was evident. The left pleural cavity contained 100 cc. of straw-colored fluid, and there were focal fibrous adhesions about the right upper lobe of the lung. The pericardial sac was distended and contained about 50 cc. of clear yellow fluid. The heart weighed 460 gm.; all the chambers were dilated; the valves were normal, and the myocardium was moderately firm and pale purple-gray. The left ventricle was 20 mm. in thickness, and the right ventricular wall was 7 mm. in thickness. The coronary ostia were patent, and their lumina revealed smooth glistening surfaces. The lungs were smaller than normal, but their weight was not reported. The surface was gray-black and less crepitant than normal, and the bronchi were slightly dilated and contained bloody mucoid fluid. The intima of the pulmonary arteries was smooth. The liver weighed 1,300 gm. and on cut section was pink-tan and mottled with yellow-brown areas, causing the markings to be barely visible. There were no other grossly abnormal findings.

Microscopic Examination.—Sections of the heart showed enlarged muscle fibers and slight increase in the fibrous connective tissue. In the lungs the alveoli were compressed, and there was an abundance of connective tissue surrounding the blood vessels and bronchi. The bronchi in places were markedly dilated and their lining epithelial cells piled up, with foci of round-cell infiltration around the bronchi. One section showed bronchiectasis of long standing. The kidneys

showed engorgement of the glomerular tufts and capillaries with blood. The liver cells were very swollen, and most of them were filled with fine and coarse fat droplets. The periportal septa were narrowed.

Diagnosis.—The anatomic diagnoses included dorsal kyphosis and scoliosis; pectus carinatum; lumbar lordosis; dilatation and hypertrophy of the left and right ventricles of the heart; compression atelectasis of the right upper pulmonary lobe; passive congestion of the lungs, spleen, and kidneys, and marked fatty changes in the liver.

CASE 3.—M. J., a 44-year-old Negro woman, was admitted to the medical service of the Cook County Hospital on Oct. 1, 1944, with a history of shortness of breath for two years, principally on exertion; orthopnea, and ankle edema for the past four months. She had been under the care of her private physician since 1943, receiving digitalis pills daily. Heart consciousness, especially on exertion, had been present intermittently for over one year. During the past 10 days the above symptoms had increased markedly in severity and she had begun to notice swelling of her abdomen. The patient's chest deformity had been present as long as she could remember.

The physical examination revealed a small poorly nourished Negro woman sitting up in bed, with a marked right scoliosis and kyphosis. Her blood pressure was 104/80, pulse rate 110 and regular, respirations 44 per minute, and temperature 99.2 F. orally. The teeth were very carious. Her lips were slightly cyanotic and the neck veins distended. The heart borders could not be percussed, owing to the chest deformity. No murmurs were heard. Basilar rales were present posteriorly. The abdomen was protuberant and tender, and a fluid wave was evident. The liver was not felt. Marked bilateral pitting edema of the ankles was present. The urine was amber, with a trace of albumin and a specific gravity of 1.013. The ECG was interpreted as showing right heart strain pattern. Hemoglobin was 86%, with 5,020,000 red blood cells, 7,100 white blood cells, and a normal differential count. X-ray of the chest showed a right scoliosis, passive congestion, and slight transverse enlargement of the heart probably due to the chest deformity. The circulation times were 18 seconds for the arm-lung with ether, and 30 seconds for the arm-tongue with calcium gluconate.

The clinical impression was cor pulmonale secondary to the chest deformity, and the patient was treated with phenobarbital, digitalis, ammonium chloride, and theophylline-methylglucamine (Glucophylline). In addition, each day the patient received 1 cc. mercurophylline injection, U.S.P. (Mercupurin), with decrease in ankle edema. However her dyspnea remained, and on the 22nd hospital day she received morphine sulfate, ⅙ grain (10 mg.), hypodermically, because of marked dyspnea and chest pain. She died 1 hour 20 minutes later.

Autopsy.—The body was that of a poorly nourished Negro woman, 44 years old, 4 ft. 10 in. (145 cm.) tall, weighing 106 lb. (47.7 kg.). The pupils were dilated and equal. The chest was deformed; the spine was greatly curved in the thoracic portion, with a sharp posterior angle and a marked curve to the right. The ribs were thrust forward and the chest cage greatly deformed, with its length reduced. The abdomen was distended and soft. The skin of the legs and feet was dry and scaly.

The heart weighed 300 gm. The epicardium was smooth and unchanged. The heart was dilated and of globular shape, with the right chambers making up much of the mass. On section the myocardium was pale red and rather soft and friable. The right ventricle was 10 mm. in thickness, and the left, 14 mm. The right cardiac chambers were markedly dilated, and the left chambers moderately so. The papillary muscles and trabeculae carneae were flattened. No valvular lesions were seen. The circumferences of the valve rings were as follows: pulmonary, 65 mm.; aortic, 60 mm.; mitral, 95 mm., and the tricuspid, 125 mm. The ostia of the coronary arteries were patent, and on section the lumina were open and the walls not thickened. Their intimae showed scattered small plaques. The left lung weighed 260 gm. and was moderately expanded and light. The pleura was smooth and showed petechial hemorrhages. On section, it was brick-red, moderately bloody, and everywhere soft and crepitant. The bronchi contained reddish sticky mucus. Their linings were unchanged. The pulmonary artery lining was diffusely yellow but smooth. The hilar lymph nodes were soft and showed only anthracosis. The right lung weighed 320 gm. and was moderately distended, light, and crepitant throughout. The pleura was smooth and unchanged. On section, it was mottled light and dark red and bloody and resembled the other lung. The pulmonary arteries, bronchi, and lymph nodes were normal.

There was 50 cc. of straw-colored fluid in the peritoneal cavity. The liver weighed 1,200 gm. On section, the tissue was mottled yellow and dark red. The centers of the lobules were dark red, and the margins were yellow, with coalescence of the adjacent lobules. The rest of the abdominal organs were not remarkable.

Microscopic Examination.—The heart on sectioning revealed hypertrophy of its fibers. In the lungs there was passive congestion and edema, and sections of the liver revealed marked passive hyperemia, with early congestion fibrosis.

Diagnosis.—The chief anatomic diagnoses included right kyphoscoliosis of the thoracic spine, etiology undetermined, with hypertrophy and dilatation of the heart, mainly of the right chambers, and chronic passive congestion of the lungs, liver, and kidneys.

CASE 4.—E. L., a 38-year-old white woman was admitted to the Cook County Hospital as an emergency case on Oct. 22, 1948. The patient's mother informed the examining physician that she had had rheumatic heart disease for the past 17 years, which responded well to five drops of digitalis twice a day. She had regularly attended the cardiac clinic of a neighboring hospital during this time. The family first discovered her chest deformity when she was five months of age, and it had progressed in severity throughout the years. The patient completed high school and college, but there was no information as to her present occupation. Five days before admission the patient experienced shortness of breath, weakness, and pounding of her heart. The day of admission the patient became markedly dyspneic, and her mother rushed her to the hospital. The past history was noncontributory, except for a mastoid operation at the age of 18 years.

The physical examination revealed a very dyspneic and cyanotic short, extremely kyphoscoliotic white woman. She was lying on her left side and expectorating pink frothy fluid. The blood pressure was 72/54; pulse rate, 140 and regular; temperature, 99.6 F. orally, and respirations, 40 per minute. Her skin was pale and warm. The neck veins were distended. Because of the extreme right kyphoscoliosis and dyspnea the heart could not be evaluated; however, a harsh apical systolic murmur was detected. There were moist inspiratory and expiratory rales in both lung bases posteriorly. Her abdomen was protuberant and firm; the liver dullness was increased inferiorly to percussion, and it was slightly tender, but the edge could not be felt. There was no ankle edema. The urine was negative for sugar, albumin, and acetone. The ECG showed right heart strain pattern and sinus tachycardia. The ward physician's impression was acute pulmonary edema and chronic cor pulmonale. She was treated with intranasal oxygen, mercurophylline injection, U. S. P., penicillin, digitoxin, aminophylline, and bloodless phlebotomy. One hour after admission patient was given morphine sulfate, ⅙ grain (10 mg.), and atropine sulfate, 1/120 grain (0.5 mg.), subcutaneously, with some subjective relief. At 10:30 p. m. the morphine and atropine doses were repeated by the ward physician, because of the patient's recurrent restlessness. She died 45 minutes later.

Autopsy.—The body was that of a fairly well-developed well-nourished white woman, measuring 135 cm. and weighing 52 kg. The face was flushed, and there was a moderate exophthalmos. The pupils were round and equal. There was slight asymmetry of the face, and the mouth was edentulous. The mucosa of the lips was cyanotic. The breasts were small. The chest was deformed. The right chest was sunken somewhat, and the left chest protruded 2 cm. above the right chest along the costochondral junction. The abdomen was distended about 2 cm. above the sternum. There was a tremendous scoliosis of the spine, an S-shaped curvature, with the first angulation to the right in the thoracic region and the second to the left in the thoracolumbar region. No pathology was noted in the vertebrae on cut section.

The heart weighed 350 gm., and the pericardial sac contained 15 cc. of clear fluid. The myocardium was pinkish-red and firm. The left ventricle measured 15 mm. in thickness, and the right ventricle measured 6 mm. The pulmonary ring was 90 mm. in circumference; the aortic ring was 70 mm.; the mitral ring was 95 mm., and the tricuspid ring was 120 mm. The endocardium was slightly thickened, especially in the auricles. There was dilatation of all the cardiac chambers, particularly the right. The coronary vessels were thin-walled and smooth. The epicardium showed numerous thickened patches measuring 5 by 2 and 5 by 5 mm. The left pleural cavity contained numerous string-like adhesions, and the right pleural cavity was free. All lobes were crepitant and heavy and fused by dense adhesions. On section, the surfaces were deep red and moist, with copious amounts of pink frothy fluid. The mucosa of

the trachea and bronchi were purplish red, covered by a mucoid reddish material. The posterior portions of both lower lobes showed atelectasis. Careful dissection of the pulmonary vessels revealed minimal intimal thickening and occasional atheromatous plaques. The liver weighed only 850 gm. and on cut section was tan-brown with fairly prominent central zones. The spleen weighed 75 gm. and on section was deep red. The follicles and trabeculae were prominent.

Microscopic Examination.—Numerous sections of the heart muscle did not reveal any abnormalities. The lung showed severe engorgement plus marked infiltration of red blood cells, leucocytes, and serum in the alveoli. The liver revealed marked cloudy swelling of the cord cells, with congestion around the central veins.

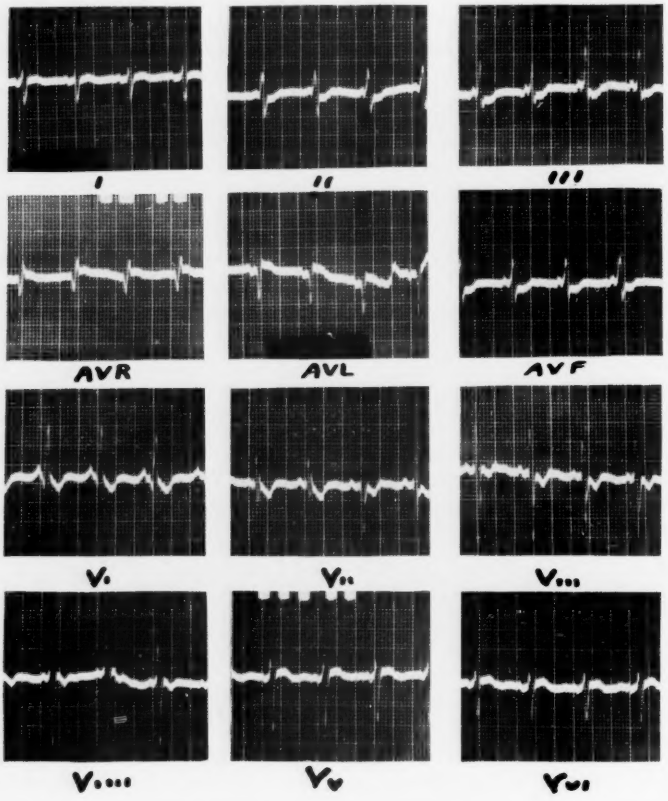
Diagnosis.—The principal anatomic diagnoses were marked right kyphoscoliosis of the spine, etiology undetermined; edema of the pulmonary lobes; fibrous adhesions of both pleural cavities; atelectasis and hemorrhagic bronchopneumonia, and passive congestion of the liver, spleen, and kidneys.

CASE 5.—W. D., a 31-year-old white man was admitted to the medical service on March 10, 1953. The patient stated that he was well until 1948, when he noted shortness of breath and swelling of ankles for the first time. This resolved on bed rest but returned last year, necessitating hospitalization, which was at another hospital. He was treated with bed rest and pills, which he took until four months before the present admission. He worked as a dishwasher until the middle of February, 1953, when the dyspnea and ankle edema returned. The patient confined himself to complete bed rest, and when his symptoms increased in severity he came to the Cook County Hospital. Systemic review was otherwise negative.

On examination he was a poorly developed well-nourished white man, orthopneic, with cyanotic lips, slight clubbing of the fingers, and marked edema of the lower extremities. There was a marked right kyphoscoliosis and pectus carinatum. His neck veins were distended. The blood pressure was 120/80, pulse rate 86, and respirations 32 per minute. The lungs were clear, and the heart borders were difficult to interpret because of the chest deformity. However, there was an apical systolic thrill, a Grade 3 harsh systolic murmur, and a suggestion of a presystolic rumble at the apex. The liver was palpable five finger breadths below the midcostal margin and was tender. There was severe sacral and leg edema. Laboratory examination revealed normal urine and blood cell count and a negative Kahn test. X-ray of the chest was interpreted as indicating hypertensive heart disease, because of the marked prominence of the left ventricular segment. Blood nonprotein nitrogen was 48 mg., and the total protein, 6.2 mg. per 100 cc. An ECG showed right axis deviation, right ventricular hypertrophy and strain pattern, and nodal tachycardia (Fig.). Rheumatic heart disease with mitral stenosis and regurgitation, with relative tricuspid insufficiency, was considered, with pulmonocardiac failure and Eisenmenger's complex to be ruled out in the differential diagnosis. The patient was treated with digitalis, meralluride, U. S. P. (Mercuhydrin), and a low-salt diet. The peripheral edema and liver distention decreased on cardiac management; however, on March 16 he complained of some substernal pain and was given morphine sulfate, ⅙ grain (10 mg.), and phenobarbital, 2 grains (120 mg.), hypodermically, with some relief. On March 17 at 8:15 p. m. this order was repeated, and the patient died two hours later.

Autopsy.—The body was that of a well-nourished white man weighing approximately 180 lb. (81 kg.) and measuring 5 ft. (150 cm.) in length. The head was normal in configuration and shape; the pupils were round and equal. The chest was emphysematous-appearing, with a chicken-breast deformity of the sternum and a marked kyphoscoliosis. The abdomen was moderately distended. The lower extremities showed 2+ pretibial edema. The peritoneal cavity contained 1 liter of straw-colored fluid, and the liver edge was three fingerbreadths below the right costal margin and four fingerbreadths below the xiphoid process. The pericardial sac contained approximately 600 cc. of straw-colored fluid. Both pleural cavities were free of fluid and adhesions. The heart weighed 600 gm., and its apex was formed by both ventricles. The left ventricle was moderately hypertrophied and dilated. The right ventricle showed marked dilatation and hypertrophy; its wall was 12 mm. in thickness. The tricuspid ring was markedly widened, as was the right atrium. The coronary arteries and aorta had smooth and shiny lumina. The myocardium was firm and red-pink. The lungs weighed 1,800 gm. and were markedly larger than normal. Their appearance was that of an air cushion, and they

showed visibly dilated alveoli and bullae. On palpation they revealed increased air content. The cut surface was dry. The tracheobronchial tree was injected and was filled with purulent material. The branches of the pulmonary arteries showed marked atheromatosis. The spleen weighed 210 gm. and had a tense capsule and a firm consistency. The cut surface was deep brown, and the pulp could not be scraped. The liver weighed 1,700 gm. and had a smooth capsule with a sharp edge. The cut surface showed red depressed central areas, many of which were fused by confluence, surrounded by paler areas. The rest of the abdominal organs and brain were not remarkable, except for congestion.



Nodal tachycardia, right axis deviation, and right ventricular hypertrophy and strain pattern.

Microscopic Examination.—There was hypertrophy of the myocardial fibers, and they were separated by loose connective tissue. In the lungs the alveoli were markedly dilated; their walls were thin and showed engorged blood vessels. In the liver the central veins were dilated and engorged with red blood cells. Several lobules revealed central necrosis, with hemorrhage and increase of fibrous tissue in the portal areas. There were no significant abnormalities in the other organs.

Diagnosis.—The anatomic diagnosis included hypertrophy and dilatation of the heart, principally of the right ventricle; dilatation of the right auricle; hydropericardium; pulmonary atherosclerosis; emphysema of the lungs; chronic passive congestion of the liver and spleen; ascites; pectus carinatum, and right kyphoscoliosis of the thoracic portion of the spine.

COMMENT

The deformity in these people has so hindered their general development that their appearance suggests dwarfism. The cardinal symptom is dyspnea, which usually occurs after the deformity reaches its maximum, usually at the age of 18 to 20 years. Mild dyspnea is usually present for several years; however, the length of time from the onset of the more acute manifestations to death is relatively short, often only several months and occasionally only a few days.

The mechanics of respiration are inefficient in kyphoscoliosis. In order to compensate for this inefficient mechanism these people increase their respiratory volume. They overbreathe and therefore suffer from the chief symptom—habitual dyspnea. Since the vital capacity is reduced by one-half or more because of the diminished capacity of the thorax, it is easily understandable why they are short of breath. The respiration is chiefly abdominal in type. The ribs move only ineffectively. The habitual dyspnea becomes progressive, so that slight exertion is distressing, and eventually there develops paroxysmal dyspnea, asthmatic wheezing, and episodes of great weakness or syncope. The transition from simple dyspnea to severe symptoms marks the onset of pulmonocardiac failure. Many develop tachycardia, although the exact mechanism for this is unknown. Boas [11] noted arrhythmias. Patients with kyphoscoliosis are subject not only to dyspnea but also to stubborn coughs and palpitation. Cyanosis is also evident, especially of the head and neck, sometimes suggesting a mass in the superior mediastinum. It is surprising that clubbing of the fingers was present in only one case (Case 5). Pulmonary infection, respiratory depressants, or any process that further reduces pulmonary function and vital capacity in the hunchback may lead to pulmonocardiac failure. Partial collapse and infection are but natural results in these poorly aerated lungs. Pneumonia, emphysema, bronchitis, bronchiectasis, and atelectasis are frequently associated, and pneumonic areas often fail to resolve in the usual manner. The mildest bronchitis may prove fatal to this type of patient, leading to asphyxia and death.

Physical findings are difficult to elicit, because of the conformation of the chest. Percussion is frequently unreliable. There are no characteristic murmurs, although a systolic murmur may be heard at the apex and base and the second pulmonary sound is frequently accentuated. In some cases the pulses are unequal, probably because of a kinking of a subclavian artery. Gallop rhythm has been frequently described. In Reid's [6] case, as in one of our own (Case 5), there was a systolic thrill at the apex and a loud blowing systolic murmur maximal at the apex and audible over the entire precordium. There was also a low-pitched diastolic murmur at the apex. This led to a diagnosis of rheumatic heart disease with mitral stenosis and insufficiency. Autopsy failed to confirm this diagnosis. Coombs [5] stated that the apical impulse was diffuse in his four cases and that in all of them a *bruit de galop* was heard. It is likely that the chest deformity causes distortion of the normal heart tones, so that frequently, because of the young age group, these patients are mistakenly diagnosed as having congenital or rheumatic heart disease. It is possible, as has been suggested by Reubi,[12] that, because of dilatation of the pulmonary valves and the right ventricle being hypertrophied and dilated, the apical presystolic murmur may be due to a functional tricuspid stenosis, which is analogous to the mechanism for the explanation of an Austin-Flint murmur in the presence of aortic regurgitation.

In most instances the x-ray reveals compression and atelectasis on the side of the deformity, while the opposite side is the site of compensatory emphysema. Both processes however, may be present in the same lung. The heart is of "mitral shape," probably as a result of enlargement of the right ventricle and rotation of the heart as a result of the deformity. Aortic anomalies, because of alterations in the course, twisting, or kinking, may burden the left side of the heart.

Since the majority of cases of pulmonocardiac failure have right auricular and right ventricular hypertrophy, the electrocardiographic pattern is, as a rule, consistent with chronic cor pulmonale. In a study of 100 cases of chest deformity without evident cardiac or pulmonary disease, Adorno [13] found normal axes in 80%. This may be explained either by a total displacement of the whole heart without rotation or by combined rotation in both longitudinal and anteroposterior axes, with neutralization because of their opposing effects.

Chapman [9] made an extensive study of respiratory metabolism in pulmonocardiac failure and found the most striking feature to be the absolute and relative reduction of lung volume. The circulation time, venous pressure, arterial pressure, and cardiac output were usually normal. When patients were exposed to a low-oxygen mixture, the respiratory minute volume was increased; hence, with a chest deformity they had to perform more work to abstract the required amount of oxygen from the inspired air.

With the recent development of the technique for recording pressures in the right auricle and right ventricle by connecting an intracardiac catheter to a Hamilton manometer, it is now possible for the first time to study some aspects of right heart function and pulmonary circulation in this type of patients. Bloomfield [14] in a series of 70 cases of chronic pulmonary disease observed only one case of kyphoscoliosis, and it is noteworthy that there was little elevation of right ventricular pressure in this patient. This is a fertile field for further study.

Theoretically, because of the increased resistance in the pulmonary circuit it would naturally follow that the pressure in the right ventricle and atrium would be elevated, with eventual hypertrophy and dilatation of these chambers. The capillary bed is further lessened by the almost constant presence of emphysema, atelectasis, and superadded chronic bronchitis. Another factor may play an important role in increasing the work of the right heart. Normally the negative pressure in the thorax during inspiration facilitates flow of venous blood into the right auricle as well as from the pulmonary capillaries to the left auricle. The elastic recoil of the lung is a further aid to the movement of blood from the right side of the heart to the left. In the patients with thoracic deformities there is a greatly limited respiratory excursion, so that this accessory aid to the circulation is rendered negligible. Dyspnea is probably first due in part to atelectasis and emphysema, and myocardial insufficiency becomes the most important factor later.

The morbid anatomy has been adequately described in the literature, and yet there is no agreement as to the effect of thoracic deformities on lung tissue. The majority of patients have dilatation and hypertrophy of the right ventricle. The dilatation of the right ventricle may be carried to the point of tricuspid insufficiency. The two branches of the pulmonary artery may become unequal because of differences in the development of each lung.

Ljungdahl [15] and Kerwin,[10] in addition to the dilatation and hypertrophy of the right ventricle observed dilatation and arteriosclerosis of the pulmonary artery

in the majority of cases. The lungs are small in most cases, probably because these people are underdeveloped. On gross study the lungs reveal emphysema, bronchitis, bronchiectasis, and pneumonia.

Significant microscopic abnormalities are strikingly lacking. Congestion, edema, and alveolar collapse are usually noted, but, surprisingly, the small pulmonary vessels are normal in appearance. Congestion of the liver, spleen, and other organs are the only other relevant findings.

It is believed that deformity of the chest is frequently not appreciated as an etiologic factor in some cases of cardiac failure. Pulmonocardiac failure is not analogous to the usual cor pulmonale and would appear to stand alone in its clinical manifestations. Because murmurs simulating rheumatic heart disease and gallop rhythm are frequently present, these cases are often misdiagnosed and the chest deformity overlooked as the prime cause of the heart failure. It is hoped that with the increased use of cardiac catheterization pressure changes in the various heart chambers may shed new light on the mechanism of this interesting condition.

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EXSUFFLATION WITH NEGATIVE PRESSURE (E.W.N.P.)

Elimination of Radiopaque Material and Foreign Bodies from Bronchi of Anesthetized Dogs

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THE ELIMINATION of radiopaque material from the tracheobronchial tree of anesthetized dogs was reported in a previous paper.[1] This was accomplished by two devices which produced high-volume expiratory-flow rates simulating the natural cough.* Studies of bronchial dynamics by serial bronchography revealed a twofold dilatation of the medium-sized bronchi in animals subjected to an inflationary pressure of + 40 mm. Hg. The restoration to normal of the blood gas values found in obstructive dyspnea, reported by Cherniack, Gordon, and Drimmer,[5] may be explained in part by the marked dilatation of the bronchi.

The development of a more effective technique, whereby there is slow inflation of the lungs, followed by an "explosive expiration," resulted in a total pressure-drop of approximately 100 mm. Hg, with expiratory-flow rates that surpassed those attainable by the most vigorous cough of normal human subjects.[6] A positive pressure blower served to inflate the lungs to a peak pressure of + 30 to 40 mm. Hg over a period of two seconds. The expiratory phase was initiated by a solenoid-activated valve, which cut in a negative-pressure blower operating at a suction pressure of — 40 to 60 mm. Hg. The resulting 100 mm. pressure-drop was attained in 0.02 second. In an extension of our previous studies, the effect of high expiratory-flow rates achieved by exsufflation with negative pressure (E. W. N. P.) on the elimination of mucin-thorium dioxide (Thorotrast) mixtures and opaque foreign bodies from the tracheobronchial passageway of anesthetized dogs has been investigated.

METHODS

Ten cubic centimeters of 24% thorium dioxide in aqueous suspension thickened with gastric mucin to the approximate consistency of viscid sputum was introduced into the right main bronchus of anesthetized dogs via a catheter threaded through a bronchoscope. Bronchograms were taken in the right lateral position immediately after filling with contrast medium and after treatment with E.W.N.P. After the control roentgenograms had been taken, the animals were intubated and an inflatable cuff provided an air-tight seal. The E.W.N.P. apparatus, fitted with a trap, was attached to the end of the intubation tube. A total of 44 dogs were employed in this study, 7 of whom served as controls and were not treated after the instillation of the radio-

These studies were supported by a grant from the National Foundation for Infantile Paralysis.

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* References 2-4.

paque material (Table). Eight animals were treated over a period of 10 to 15 minutes with a hand-operated solenoid device, being "coughed" intermittently on an average of 60 times at a pressure setting of + 30 mm. Hg on inspiration and — 40 mm. Hg on expiration. The inflationary positive pressure was preset for a gradual build-up over a two-second period. Twelve dogs were treated with an automatic pressure-controlled two-motor apparatus with a pressure setting of + 40 mm. Hg on inspiration and — 60 mm. Hg on expiration. Each of these dogs was "coughed" a total of 36 times in six minutes.

The effect of this greater velocity of air movement accompanying a pressure drop of 100 mm. Hg produced by the E.W.N.P. apparatus on foreign bodies introduced into the bronchi of anesthetized animals was studied in 17 additional dogs. Eight of the 17 animals were mechanically "coughed" within two hours after instillation of the foreign bodies, which consisted of lead balls measuring 4.5 mm. in diameter and weighing 0.6 gm.; safety pins, 1.5 cm. in length and 0.4 cm. in width, or steel screws, 1.3 cm. by 0.3 cm. in dimension, used alone or in combinations. Some of the animals had as many as five lead balls inserted simultaneously into the right main bronchus. Three dogs each had a safety pin in addition to the lead balls, while two had screws introduced. Posteroanterior and lateral x-ray films were taken before and after treatment.

Experimental Procedures in Anesthetized Dogs Treated with Exsufflation with Negative Pressure (E.W.N.P.)

Dogs, No.	Radiopaque Substances	E.W.N.P. Device	Interval Between Bronchial Insertion and E.W.N.P.
7	Mucin-thorium dioxide	None	Controls, untreated
8	Mucin-thorium dioxide	Manual	½-2 hr.
12	Mucin-thorium dioxide	Automatic	½-2 hr.
8	Foreign bodies *	Automatic	1-3 hr.
9	Foreign bodies *	Automatic	1-4 days

* Lead balls, safety pins, and steel screws.

In order to observe the effect of E.W.N.P. on foreign objects which had been retained in the tracheobronchial passageway for varying periods of time ranging between one and four days, an assortment of metallic objects listed above were placed in the right bronchus of the remaining nine dogs and left in situ: It was believed that the inflammatory reaction and edema provoked by foreign bodies retained over 24 hours would more closely simulate the conditions common in humans in whom aspirated foreign material is often undetected for several days. Prolonged retention of metallic objects proved more difficult than was anticipated. Upon recovery from anesthesia, the dogs would invariably cough up the foreign bodies, and attempts at depressing the cough reflex with meperidine (Demerol) were ineffective. The problem was solved by layering each foreign body behind a tightly packed plug of absorbable gelatin sponge, U. S. P. (Gelfoam). By this method, lead balls and safety pins were retained for as long as four days.

RESULTS

The effectiveness of exsufflation with negative pressure in eliminating radiopaque material from the tracheobronchial tree was measured by the amount of viscid thorium dioxide-mucin mixture collected in the trap and rubber tubing and an evaluation of the bronchograms taken after treatment. It was estimated that 75 to 90% of the radiopaque material had been eliminated in the eight dogs treated with the hand-operated device, which developed a total pressure drop of 60 to 70 mm. Hg in 0.04 second. The 12 animals treated with the automatic, two-motor apparatus, in which a pressure drop of 100 mm. Hg over a 0.02 second interval is produced, had virtually 100% elimination of the thorium dioxide within a period of six minutes. This is illustrated in the bronchograms of a dog before treatment

and after six minutes of E. W. N. P. (Fig. 1). The bronchograms of the control animals taken after a lapse of 15 minutes to 2 hours revealed no change when compared with the films taken immediately after instillation of the thorium dioxide-mucin suspension (Fig. 2).

In each of the eight dogs who were "coughed" by E. W. N. P. shortly after insertion of the foreign bodies, complete elimination occurred following 18 to 36 exsufflations. Representative chest films demonstrate the removal of a pin and lead ball from the right lower lobe and two lead balls from the right upper lobe (Fig. 3).

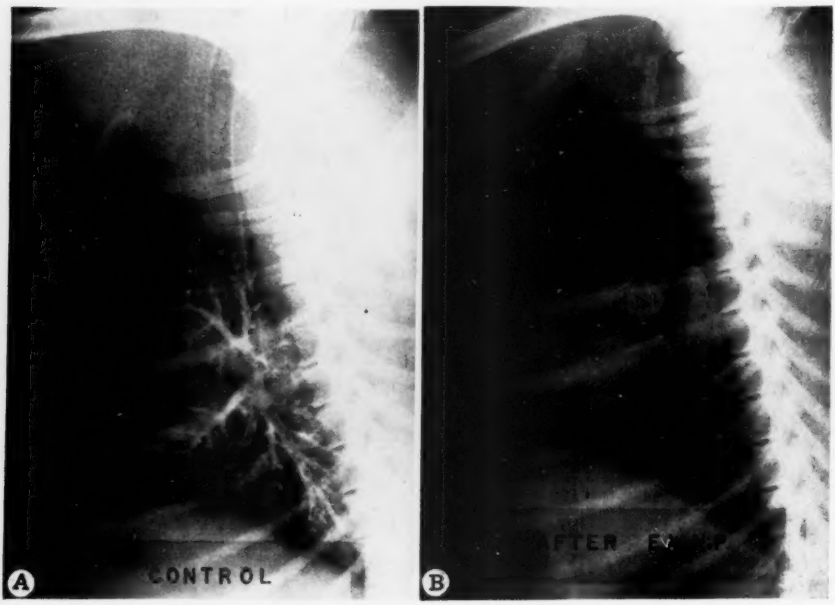

Fig. 1.—Bronchograms revealing virtually complete elimination of the mucin-thorium dioxide suspension after six minutes of treatment with E.W.N.P.: *A*, control; *B*, after E.W.N.P.

Of the remaining nine animals treated for retained foreign bodies, two were coughed 24 hours after bronchoscopic introduction, with removal of a pin in one dog and four of the five lead balls in the other. Complete elimination of retained objects was accomplished two days after insertion in two other dogs. Similar success was achieved with foreign bodies retained for three days in two more animals, while one dog was treated four days later, with complete recovery of five lead balls. There were two failures in these long-term experiments; in one a screw and in the other a pin had become wedged at right angles to the longitudinal axis of the right main bronchus. Roentgenograms taken immediately after insertion of the foreign bodies, before treatment three days later, and after E.W.N.P. are shown in Fig. 4. The number of exsufflations required to eliminate the foreign bodies ranged between 6 and 60, with a mean of 24 "coughs" being effective. Fluoroscopic observation during E.W.N.P. revealed that inflation of the lung took place beyond the

region of the metallic object on inspiration without causing its displacement. The negative-pressure phase initiated the movement of the foreign body towards the hilum.

Bronchoscopic inspection of the trachea before treatment usually revealed considerable mucosal edema and inflammation, which subsided following removal of the foreign bodies. Many of the chest films of the dogs in which metallic objects had been retained for three or four days showed increase in density of the lung field adjacent to the foreign bodies. Serial chest films taken after therapy with E.W.N.P. and one and two weeks later showed complete clearing. Exsufflation with negative pressure appeared to be well tolerated by all the animals. Hyper-

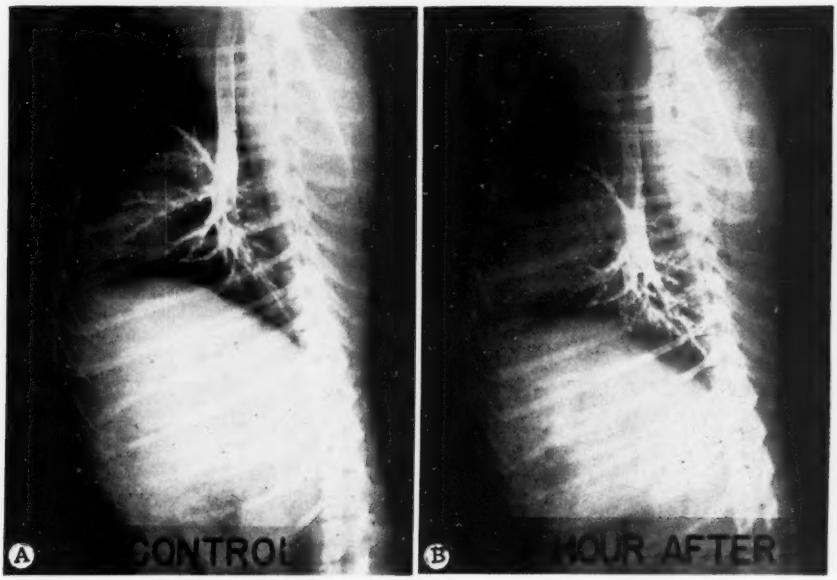

Fig. 2.—Roentgenograms of control animal, which demonstrate no emptying of the contrast medium after one hour; *A*, immediately after insertion of mucin-thorium dioxide suspension; *B*, one hour later.

ventilation was noted in each instance and resulted in a brief period of apnea following cessation of "coughing." The two animals in which E. W. N. P. failed to remove the impacted foreign bodies after four days were observed to have a persistent cough. It was noted that the dog with the retained pin stopped coughing on the 10th day after insertion, and x-ray examination showed no evidence of foreign body. The second animal showed increasing consolidation in the right lower lobe and died two weeks after insertion of the screw. Necropsy findings confirmed x-ray evidence of a bronchopneumonia of the right lower lobe. Several animals in whom therapy with E. W. N. P. had resulted in successful elimination of either foreign bodies or the mucin-thorium dioxide suspension were killed, and careful examination of the lungs revealed no evidence of parenchymal damage, i. e., hemorrhage, alveolar tears, or emphysematous blebs.

COMMENT

Barach and Beck [7] recently reported 76 patients with respiratory insufficiency associated with the retention of bronchial secretions who were treated with E. W. N. P. The elimination of large amounts of sputum and mucus plugs resulted in

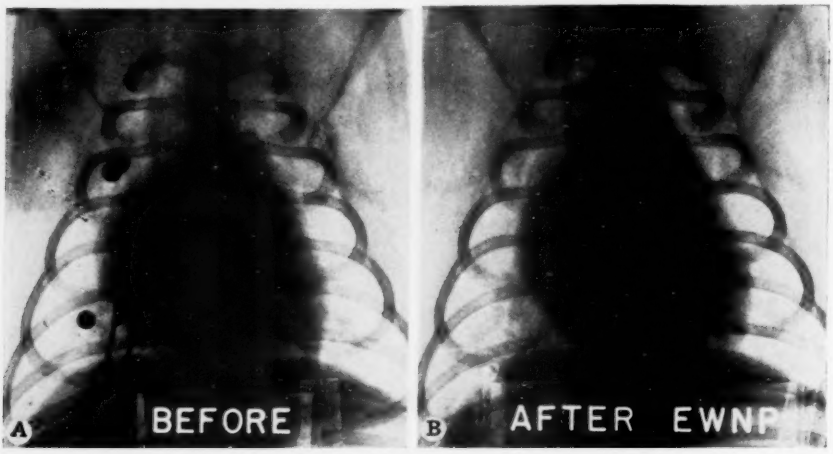

Fig. 3.—Representative chest films which demonstrate the removal of a safety pin and a lead ball from the right lower lobe and two lead balls from the right upper lobe bronchus after 36 exsufflations with E.W.N.P.: *A*, before E.W.N.P.; *B*, after E.W.N.P.

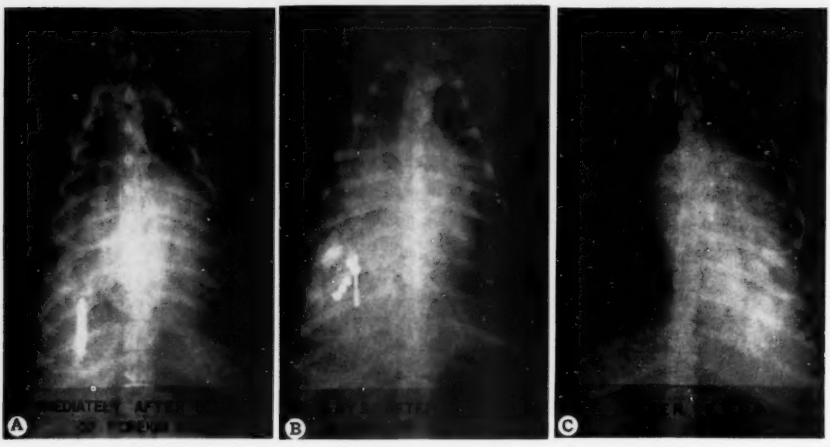

Fig. 4.—Roentgenograms showing visualization of foreign bodies three days after insertion via a bronchoscope and their subsequent removal by E.W.N.P.: *A*, immediately after insertion of foreign bodies; *B*, three days after insertion of foreign bodies; *C*, after E.W.N.P.

clinical improvement associated with an increase in the vital capacity in 34 patients. The extent to which E. W. N. P. will facilitate emptying of the tracheobronchial tree is demonstrated in the bronchograms of the dogs taken before and after treatment. The viscosity of the mucin-thorium dioxide mixture employed in these

animals appeared to be grossly comparable to the viscid sputum commonly encountered in patients with pulmonary emphysema and bronchiectasis.

A comparison of the mask-pressure tracing obtained with a Statham strain gauge revealed that E. W. N. P. produced a greater and swifter expiratory pressure drop than the exsufflator alone and that this was accompanied by a much higher velocity of air movement (Fig. 5). In an earlier experiment, employing the simple exsufflator attached to a tank respirator, it was demonstrated that a steel ball was removed from the right lower lobe bronchus to the left hilar region of the dog's lung. The greater effectiveness of E. W. N. P., which is capable of expiratory flow rates of 20,000 cc. per second at a pressure drop of 100 mm. Hg over exsufflation alone, was especially evident in those studies in which foreign bodies were removed from the lung.

The successful elimination of radiopaque objects from the bronchi of these experimental animals was facilitated by intubation and provision for a leakproof airway, so that pressure changes could be directly transmitted to the pulmonary

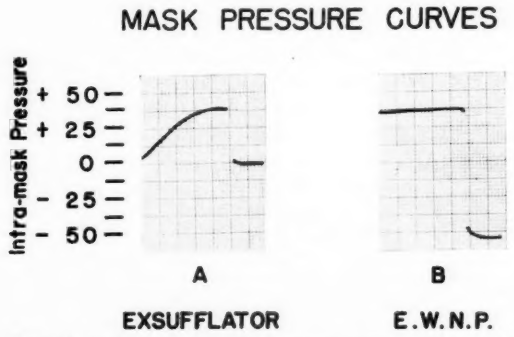

Fig. 5.—Graphic tracings of the mask-pressure curves obtained with a Statham strain gauge: *A*, a gradual rise in pressure to 40 mm. Hg above atmospheric pressure followed by a swift fall to atmospheric pressure, in 0.06 second, with simple exsufflation; *B*, a total drop of 90 mm. Hg pressure, 40 mm. above and 50 mm. below atmospheric pressure, accomplished in 0.02 second with E.W.N.P.

structures with minimal loss. The clinical applications of this form of "mechanical coughing" in the removal of aspirated foreign material would appear feasible, employing a suitable mask in the conscious, cooperative patient and an endotracheal tube in the unconscious subject.

SUMMARY

Studies are reported on the effect of high expiratory flow rates achieved by exsufflation with negative pressure (E. W. N. P.) on the elimination of mucin-thorium dioxide (Thorotrast) mixtures and radiopaque foreign bodies from the bronchi of anesthetized dogs.

Bronchograms taken immediately after instillation of the viscid thorium dioxide suspension thickened with gastric mucin and immediately after treatment demonstrated that

1. Approximately 75% of the thorium dioxide mixture was eliminated in eight dogs "coughed" an average of 60 times in 10 to 15 minutes when the total expiratory pressure drop was 60 mm. Hg.

2. Virtually complete elimination of the radiopaque material was effected in the remaining 12 animals "coughed" a total of 36 times in six minutes when the expiratory pressure drop was 100 mm. Hg.

Foreign bodies, consisting of lead shot, safety pins, and steel screws, alone or in combination, were inserted by bronchoscope into the right main bronchus of 17 dogs. In the eight animals treated by E. W. N. P. within two hours after insertion of the metallic objects, complete elimination occurred after 18 to 36 exsufflations. In seven of the nine remaining animals, treated from one to four days after introduction of the foreign bodies, successful evacuation took place after approximately 24 "coughs." The two failures in this series were attributed to the foreign objects becoming wedged in the bronchial tree.

The clinical application of E. W. N. P. in patients with a weak or absent cough reflex is useful not only in cases in which respiratory distress is precipitated by retained secretions but also in instances in which foreign matter has been aspirated into the lung and fails to mediate a cough response.

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FURTHER EVALUATION OF HYDRALAZINE IN TREATMENT OF HYPERTENSIVE DISEASE

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HYDRALAZINE has come into wide use in treatment of hypertensive disease during the past two years. Opinions as to its usefulness, practicality, and even as to its effectiveness are still widely varied. Thus, we [1] found that one-half of a group of patients, many of them with severe disease, responded favorably to its administration over periods of 3 to 12 months; more recently, Hilker, Rhoads, and Billings [2] reported a similar incidence of benefit and recommended the drug as a moderately effective antipressor agent useful in office practice. Johnson [3] found it an effective hypotensive agent in 65% of his patients treated on an ambulatory basis. However, others * find it of limited value; some use it largely as an adjuvant in association with other antipressor drugs,† and some [9] consider it quite ineffective.

In this report we shall describe observations in our previously studied patient group which will demonstrate the effect of 14 further months of treatment with hydralazine as the sole antipressor drug. These observations will form the basis for recommendations as to the use of this drug in practice and may also clarify some of the discordant opinions as to its value.

METHOD OF STUDY

Eighty-six of the original 97 patients were alive at the time of our last report. The course of all of these has been followed in the 14 months since that time; all who had responded favorably to hydralazine continued to use this drug as the sole antipressor agent; the drug was also continued in some of these who did not respond in the first period of observations.

Most of the patients were hospitalized at intervals for brief periods of study. Many were seen at frequent intervals as outpatients, and some supplied interval records of daily blood pressure, taken by the patient, by a nurse, or by a relative.

The clinical and laboratory study was as previously described[1] and formed the basis for the estimation-of-severity index. This composite is assembled from four panels, namely, diastolic pressure and the relative status of cardiac, renal, and cerebrovascular functions. In each panel the maximum score was 4; under the category of diastolic pressure, grading was 0 (less than 95 mm. Hg), 1 (96 to 110), 2 (111 to 125), 3 (126 to 140), and 4 (140 or more). Cardiac status was estimated from functional classification, physical signs, the teleoroentgenogram, and

From the Research Division of the Cleveland Clinic Foundation and the Frank E. Bunts Educational Institute.

* References 4 and 5.

† References 6-8.

the electrocardiogram; renal grading was in terms of relative proteinuria, hematuria, maximum urinary specific gravity, renal plasma flow (from the plasma clearance of *p*-aminohippuric acid), and glomerular filtration (from the clearance of mannitol); cerebrovascular status was graded from inspection of the retina and retinal vessels and from the presence of symptoms or signs of cerebrovascular dysfunction. The maximum attainable score is 16. The range of scoring in this group prior to treatment was 2.2 to 16, with a mean of 8.6.

Dosage of hydralazine was usually 400 to 800 mg. daily, divided in four doses. The response to hydralazine was graded in terms of the severity index and in terms also of diastolic arterial pressure. The response of diastolic pressure to treatment was formerly graded in four classes; this fine gradation now seems unnecessary. The patients were therefore classified for purposes of this report into two response groups; those who attained diastolic pressures persistently below 110 mm. Hg were considered to be responders, and those who failed to reach this level were classed as nonresponders.

The clinical classification of hypertensive disease[3] into groups according to major apparent etiological factors, previously described,[1] is continued in this report.

RESULTS

Fifty-four of the 86 patients on whom this study is based were classed as responders to hydralazine in the former study group; among these, 5 lost their responsiveness after one year's treatment and are now classed among the nonresponders.

TABLE 1.—*Severity Index and Mortality Rate*

	Patients, No.	Mean Pretreatment Severity Index	Patients Dead of Vascular Disease		Length of Treatment, Mo.	
			No.	%	Av.	Range
Responders	43	8.2	3	7	22	14-30
Nonresponders	32	9.0	11	34.0	13	2-24

Two responders were unable to continue treatment because of the rheumatic and febrile state described elsewhere[10]; two other responders voluntarily discontinued treatment and succumbed to cerebral hemorrhage some four months afterward; two of the responders died of extravascular causes, one of carcinomatosis and one of cryptogenic peritonitis; two who had manifested responses are not available for examination. Thus, there remain for this study 43 patients who continue to be classed as responders and who have been under continuous treatment with hydralazine.

1. *Severity, Response, and Mortality.*—The mean pretreatment severity index (Table 1) of the 43 responders was 8.2; this is nearly the same as that (9.0) of the 32 nonresponders.

Among the responders, 3 (7%) have died of vascular disease. The first of these to die was in renal failure when he was first seen. His urea clearance was about 20% of average normal, and azotemia was present. Palliative treatment by diet and control of hypertension with hydralazine enabled him to continue in active dental practice for 23 months, when he died suddenly after a convulsive seizure. The second patient had a long history of severe vascular disease; this included a phase in which his syndrome of malignant hypertension was treated with pyrogen; he subsequently sustained an intracerebral hemorrhage before treatment with hydralazine. He died of a second intracerebral hemorrhage in the 17th month of hydralazine treatment. The last, a man of 45 years, died presumably of a myocardial infarct, in the 20th month of treatment.

In contrast, 11 of the 32 nonresponders (34%) have died of vascular diseases within 6 to 19 months (mean, 13 months) after the initiation of unsuccessful treatment with hydralazine. The causes of death among those who died were cerebral hemorrhage (three), renal failure (three), and heart failure (two); three died suddenly, presumably of myocardial infarction.

TABLE 2.—*Comparison of Casual, Hospital, and Home Blood Pressures in Patient 5**

	Means and Ranges of Pressures, Mm. Hg†	Conditions of Observations	Duration of Observations, Mo.
1	180/120 (200/150-150/110)	Hospital (pretreatment)	1.5
2	152/92 (160/100-130/80)	Home (on treatment)	19
3	200/110 170/110 190/120	Outpatient casual pressures (on treatment)	2 13 14
4	153/97 (160/110-134/86)	Hospital (on treatment)	..

* Observations in Patient 5 demonstrating the close correspondence of home (2) and hospital (4) pressures during treatment and the seeming ineffectiveness of treatment had only hospital control (1) and isolated casual office (3) pressure readings been available at various intervals after the patient had come under observation.

† Pressure data in parentheses are ranges of observations in the hospital and home periods.

TABLE 3.—*Summary of Observations in Five Representative Patients*

Patient No.	Observation Period, Mo.	Average Blood Pressure, Mm. Hg	Fundus		Relative Heart Size	ECG	Urine Protein, Gm./24 Hr.	Urine RBC, Millions in 12 Hr.
			Papilledema, Grade	Hemorrhage, Grade				
1	Control	220/150	4+	3+	+12	Left ventricular preponderance	5.3	0.53
	6	95/50	0	0	0	Normal	0.02	0.0
	19	90/50	0	0	−5	Normal	0.06	0.42
2	Control	170/110	0	2+	+10	Left ventricular preponderance	0.04	0.7
	14	135/75	0	0	+5	Normal	0.02	0.34
	23	130/80	0	0	0	Normal	0.02	0.30
3	Control	180/120	2+	1+	+20	Left axis deviation	0.36	5.5
	16	150/90	0	0	+24	Normal	0.01	0.69
4	Control	190/120	1+	1+	+25	Left ventricular preponderance and strain	0.21	5.2
	12	175/95	0	0	+25	Left ventricular preponderance and strain	0.30	1.4
	27	185/100	0	0	+25	Left ventricular preponderance and strain	0.4	2.1
5	Control	180/115	0	1+	0	Left ventricular preponderance	0.1	0.23
	10	150/90	0	0	+10	Right bundle branch block	0.08	0.2
	22	150/90	0	0	+10	Right bundle branch block	0.06	0.15

In brief, starting with two groups whose hypertensive disease is of about equal severity, mortality from vascular causes is about five times greater among nonresponders than among those who respond to continuous hydralazine therapy.

2. *Arterial Pressure.*—Diastolic arterial pressure among responders ranges, by definition, under 110 mm. Hg and is usually within normal limits.[11] As previously reported, systolic pressures commonly persist at moderately hypertensive levels, of 160 to 180 mm. Hg. This systolic hypertension usually receded as treatment was prolonged. However, emotional tension, such as extreme domestic concern, or even

the outwardly minor stress of an outpatient visit, sometimes precipitates in susceptible patients an elevation of arterial pressure to hypertensive levels, such as 200/120 or 210/124 mm. Hg, far beyond the levels averaged from home blood pressure records (Table 2). That these crises of hypertension were transitory was established by reference to the home pressures, confirmation of the accuracy of the latter from means and ranges of pressures taken during brief periods of hospitalization, and, indirectly, by the continuous regression of evidences of hypertensive vascular disease.

The courses of five patients in the favorable response group are summarized in Table 3 from observations made before treatment, at the time of our previous report, and in the preparation of this one. Previously described are the relatively prompt decreases of arterial pressure and remissions of retinopathy; among the evidences of remission observed over long periods, the most striking is the progressive decline in nephrosclerotic activity, as evidenced by diminishing proteinuria and hematuria.

TABLE 4.—*Effects of Treatment on Severity Index Among Responders*

	Severity Index				
	Blood Pressure	Cardiac	Renal	Cerebral	Total
Before treatment	2.36	1.62	1.89	2.41	8.2
After 12 mo.	0.6	1.33	1.38	1.35	4.7
After 24 mo.	0.6	1.31	1.17	1.28	4.4

TABLE 5.—*Hydralazine Response and Clinical Classification*

Hypertension Classification	Patients, No.	Responders, No.	Nonresponders, No.
Early essential	5	3	2
Severe essential	18	9	9
Malignant phase	13	9	4
Renal	5	0	5
Diencephalic	8	6	2*
"Ancestral"	16	13	3
Total	65	40	25

* Complicated by renal disease.

3. *Severity Index.*—The group of responders (Table 4), previously described as evidencing a decrease in severity index, on the average maintained this improvement as long as the treatment was continued or as long as it remained effective. Progressive improvement in severity index in some was attributable largely to improved renal status. The numerical index of cardiac status showed no tendency for delayed improvement, although it should be noted that some who had required sodium restriction because of congestive heart failure were able to revert to normal diets without a recurrence of this disability. The cerebrovascular status index showed some trend toward progressive improvement (control, 2.4; at one year, 1.35, and at two years, 1.28). While this represents the average course, it should be noted that two patients (aged 60 and 63), who had previously sustained strokes, exhibited progressive cerebral deterioration during treatment and that one responder with severe diabetes mellitus sustained a stroke during treatment.

No improvement in over-all severity index or in any of its constituent panels was observed in those who were classed as nonresponders.

4. *Clinical Classification and Responsiveness.*—In our former report it was suggested that those patients were most susceptible to the favorable effects of hydralazine whose hypertension, to clinical impression, seemed to be predominantly psychogenic or neurogenic, while the incidence of response was lower in patients whose hypertension seemed to be predominantly of renal origin. Observations over a longer period confirm these associations. Thus (Table 5), of the 29 patients classed as having early essential hypertension, either diencephalic or "ancestral," 22 were classed as responders; of the 2 patients with the diencephalic syndrome who did not respond, both suffered also from chronic pyelonephritis and 1 had undergone unilateral nephrectomy. None of five patients classed as having primary renal hypertension responded favorably. That nephrosclerotic disease as such need not deter one from attempting therapy with hydralazine is shown by the fact that 9 of 13 patients who exhibited the syndrome of malignant hypertension are classed as good responders and have resumed their social and gainful activities.

COMMENT

1. *Effectiveness.*—The data confirm our previous observation that roughly half of a group of patients with hypertensive disease respond favorably to continuous treatment with hydralazine as the sole antipressor agent; they also show that such responses may be maintained in most for as long as 30 months. Thus, it seems that hydralazine is more than a moderately effective antipressor drug; in individual patients, it is usually either definitely effective or quite ineffective; it is moderately effective only in terms of an average of the group as a whole, responders plus nonresponders.

The favorable response is demonstrable in terms of decreased diastolic pressure and sustained improvement in the other panels which contribute to severity index. As previously reported, renal status improves most, cerebrovascular status next, and cardiac status least. That cardiac status improved seems likely: as noted, several patients who required sodium restriction early in the course of treatment have since been able to tolerate diets of normal sodium content. But the most dramatic evidence of the efficacy of the drug is the decreased mortality among responders as compared with nonresponders of similar physical status.

2. *Clinical Classification and Response.*—The distribution of responses among patients confirms and extends our former suggestion that "the relatively high incidence of good responses in patients whose hypertension could be presumed to be predominantly neurogenic accords with the concept that the drug may act specifically on a pathogenetic cerebral humoral pressor mechanism." Thus, also, Bein, Gross, Tripod, and Meier [12] summarize present knowledge of the pharmacology of hydralazine by concluding that its depressor effect is mediated through a specific influence on central nervous regulatory mechanisms and not, as has sometimes been assumed, through a direct effect on peripheral vessels or on known humoral pressor agents.

3. *Determination of Response.*—The primary criterion of a favorable response is a decrease of average diastolic arterial pressure. The pressures averaged for this study were means of pressures measured twice daily in hospital, of pressures similarly measured in the home by the patient or some of his relatives, and, in a few instances, of pressures measured at frequent outpatient visits. Data from several patients,

exemplified in Table 2, demonstrate that response cannot be satisfactorily evaluated by infrequent casual pressures taken in office or outpatient department. Those patients who respond best tend to be labile in their emotions and tense and anxious during physical examination. The drug does not counter the transient upward swings of pressure which result from these states of tension; consequently, reliance on isolated determinations of blood pressure may be quite misleading as to the actual average effect of the drug.

4. *Side-Effects.*—The transitory nature of most of the side-effects was also confirmed in this study. It seems likely that two major mechanisms participate in responses to initial intravenous or oral medication with hydralazine. The primary mechanism, which persists and accounts for the favorable effect of prolonged treatment, could be the suggested central depressor action of the drug. A subsidiary, transitory mechanism might depend on the inhibition of diamine oxidase (histaminase).[13] Inhibition of diamine oxidase results in hyperresponsiveness to normal concentrations of blood and tissue histamine; this would account for the flush, headache, facial and dependent edema, and some of the tachycardia, palpitation, increased cardiac output, and renal vasodilation observed after initial intravenous or oral dosage. However, most enzyme inhibitors characteristically lose their effectiveness as treatment is prolonged. Such appears to be the case with hydralazine, and this may explain the transitory nature of the side-effects.

5. *Therapeutic Procedure.*—As indicated above, it seems likely that the divergent opinions concerning the usefulness of hydralazine stem in part from differences in the approach to the use of the drug.

A prime objection to the drug, one which all but forestalled further clinical trial after Reubi's pioneering experience with it,[14] is the frequency of distressing side-effects. This, like the initial discomfort of rice and low-sodium diets, imposes an added burden on patient and physician; as with the diets, it has no necessary bearing on the desirability or practicality of prolonged therapy.

The fact that only about half of a group of patients ‡ respond favorably partly explains the infrequency and unsatisfactory character of responses observed in certain small groups of patients § and the need that some ‖ feel for supplemental antipressor medication. Reliance on casual arterial pressures probably accounts for some reported "failures."

But the commonest reason for dissatisfaction with the drug is impatience on the part of the physician, who may have become accustomed to the almost predictable initial depressor effect of such an agent as hexamethonium and tends to judge hydralazine by this standard. The fact is that many patients who ultimately respond favorably may have to be carried through several uncomfortable weeks before this therapeutic effect is observed. Lastly, some have reported the development of irresponsiveness to the drug; this was uncommon in our patients (5 of 54); this low incidence may be due to the relatively large doses we have used; conceivably the onset of true irresponsiveness to large doses may reflect a change in the mechanism which sustains the hypertension.

‡ References 1-3 and 15.

§ References 5 and 9.

‖ References 6-8.

Thus, in brief, the drug is effective, side-effects are usually controllable and transitory, tolerance is not frequent, and the dissatisfaction which others have expressed can be explained in various ways which do not diminish the value of the drug in suitable cases.

The problem then is the selection of cases and appropriate administration of the drug. In general, favorable responses occur most commonly in patients with early established essential hypertension and in diencephalic or seemingly neurogenic types of hypertension; responses occur at lower-dose levels in patients with less advanced hypertensive vascular disease. The disadvantages of treatment with hydralazine are such that it is not indicated in patients with early hypertension which can be controlled by other means or who show no signs of vascular damage. The clinical classification of types of hypertension rather that the severity of hypertension as such is a partial guide in the selection of patients for treatment with hydralazine. Severity becomes a problem only in patients with rapidly advancing malignant hypertension, not because these may not ultimately respond but because the response may be so delayed that they die before the response becomes manifest. This type of patient should presumably be treated by other means, such as with hexamethonium or with hexamethonium and hydralazine in combination, with the aim of ultimately discontinuing the ganglionic blocker as the hydralazine response appears.[16]

The schedule of treatment remains as in our previous report, viz., 25 mg. four times daily, increasing by slow increments to 800 mg. daily or until the desired effect is obtained at lower dosage; treatment is continued for eight weeks before the trial period can be considered complete. Side-effects are controlled during this time partly with antipyretics, such as acetylsalicylic acid, and with antihistaminics, but the largest factors in their control are the patient's understanding and the physician's interest and confidence. The importance of the technique of taking blood responses is noted above.

The rheumatic and febrile syndrome which appears in some patients maintained on large doses of hydralazine for long periods is fully described elsewhere.[10] Its mechanism seems quite distinct from that of the side-effects commonly experienced and may differ qualitatively from the usual drug hypersensitivity. Its occurrence emphasizes the desirability of our former recommendation that as soon as practical after a "floor" of diastolic pressure at the larger dose levels is attained dosage should be gradually reduced to whatever minimum will maintain this maximum therapeutic effect. This minimum is sometimes quite small, e. g. 200 mg. daily in patients who had required 800 mg. daily for the initial response. Dosage of 50 mg. four times daily seems, to this date, completely and indefinitely tolerable.

SUMMARY AND CONCLUSIONS

A reappraisal of a group of patients treated with hydralazine confirms the fact that about half the patients respond favorably to the drug and shows that the response may persist for as long as 30 months.

A favorable response is reflected not only in reduction of diastolic pressure to levels averaging less than 110 mm. Hg but also in improved renal, cerebrovascular, and cardiac status and, most impressively, in decreased mortality, which among responders is about one-fifth of the rate among nonresponders.

The observations confirm the association of favorable responses to hydralazine with a hypertensive disease which seems predominantly neurogenic and are consonant with the conjecture that hydralazine may suppress a central vasopressor mechanism.

Discordant views on the effectiveness of hydralazine in the treatment of hypertensive disease seem attributable to various factors. One is the fact that a large proportion of patients do not respond; another is impatience in the desire for a prompt depressor effect; another, overestimation of the significance of side-effects; another, the lack of an ordered schedule of treatment, and, last in order but not in importance, reliance on casual office or outpatient blood pressure determinations in evaluating response.

A regime of therapy is outlined by which dosage is slowly increased to 800 mg. daily, or to any lower fully effective dose, and slowly reduced thereafter to the minimum dose which will maintain the hypotensive effect.

Miss Enid Davy, R.N., and Miss Sophia Barsick, R.N., participated in this study. The hydralazine was supplied by Dr. F. Yonkman, Ciba Pharmaceutical Products, Inc., Summit, N. J.

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SOME RELATIONS BETWEEN PULMONARY EDEMA AND PULMONARY INFLAMMATION (PNEUMONIA)

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THE FREQUENT association of pulmonary edema and pneumonia in postmortem material is well known. This finding has usually been considered a mere coincidence and is often classified as a "terminal" finding. The use of the term "terminal" has in a sense been unfortunate, since it has served and sufficed as an explanation for the frequent simultaneous occurrence of these two pathological processes. Thus there has been a tendency to avoid an attempt to answer several important questions raised by the frequent concurrence of pulmonary edema and pneumonia in pathological material. These questions include the following:

1. Is the frequent simultaneous occurrence merely a coincidence or is there a pathophysiological relationship between pulmonary edema and pulmonary inflammation?

2. If such a relationship exists, does it only occur in the dying or does it also obtain in those who recover and, if so, under what conditions?

3. Are there any therapeutic or prophylactic implications to be drawn from such a relationship?

This paper will attempt to frame at least a partial answer to these questions.

METHODS

Our interest in the problem of the interrelationship of pulmonary edema and pneumonia originated in the observation of patients who appeared to have one or another of these processes. We were surprised at how frequently autopsy revealed extensive lesions of both types. We were also impressed with several patients who presented clinically what seemed to be classic pulmonary edema. Autopsy revealed chiefly pneumonia.

We therefore reviewed the charts and postmortem findings of all patients who had a pathological diagnosis of pneumonia or pulmonary edema or both during the past 10 years (1942-1952) at the Peter Bent Brigham Hospital. It soon became obvious that the major problem was one of a plethora rather than a paucity of material for analysis. It also was clear that statistical analysis would be inadequate in assessing a possible relationship between these two processes. We therefore tried

This study was made during the tenure of a Life Insurance Medical Research Fellowship (Dr. Robin).

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to select cases which either suggested or illustrated concepts involved in the relationships between these two entities. Our third source of material has been accumulated in reviewing some of the pertinent literature. Finally, we have attempted to fit all the above material into currently accepted pathological and physiological concepts.

BASIC CONCEPTS

A. *Pulmonary Edema.*—Pulmonary edema may be defined in a most general and basic way as an excessive accumulation of edema fluid in the pulmonary parenchyma. For example, Henneman [1] has defined acute pulmonary edema as a "syndrome characterized by the rapid flooding of the lung alveoli with serous or serosanguinous fluid." The clinical concept of pulmonary edema is that it is a syndrome due to excessive alveolar fluid and manifested by severe dyspnea, moist bubbling rales, hyperpnea, mounting cyanosis, frothy sputum, severe coughing, a fairly consistent x-ray picture, and frequent response to such therapeutic measures as central nervous system depression, phlebotomy, oxygen, and digitalis. Although this is the classic picture of pulmonary edema to the clinician, it must be realized that pulmonary edema can occur without all of the above findings and even without any of them.

To the pathologist, pulmonary edema is characterized grossly by heavy lungs which exude abnormal quantities of fluid when cut and microscopically by the presence of eosinophilic-staining material in the respiratory spaces of the lung without significant evidence of inflammation.

Finally, to the pathophysiologist, pulmonary edema is a syndrome characterized by increased intrapulmonary fluid resulting from diverse mechanisms. Such fluid may be produced by increased transudation or exudation of fluid, which in turn may be brought about by increased pulmonary capillary pressure, increased pulmonary capillary permeability, decreased oncotic pulmonary vascular pressure, and, conceivably, by decreased fluid resorption.[2]

Historically, acute pulmonary edema connotes to the clinician some form of cardiac failure. This viewpoint has been shown to be untenable by the wide variety of etiological factors that can result in acute pulmonary edema, many of which are obviously unrelated to cardiac factors.* Recent work has stressed the role of central nervous system and vasomotor reflexes in the pathogenesis of pulmonary edema.† However, it seems clear that any factor which increases pulmonary capillary pressure, increases pulmonary capillary permeability, or alters the rate of fluid transfer across the pulmonary capillary wall may produce pulmonary edema.

B. *Pneumonia.*—Pneumonia may be simply defined as any inflammatory lesion of the pulmonary parenchyma. The clinical picture and pathological features of this process have been so clearly established that no elaborate discussion is necessary to elucidate the semantic and nosological basis of the term pneumonia.

C. *Interrelations of Pulmonary Edema and Pneumonia.*—The observation that pulmonary edema and pneumonia occur together frequently is not a new one. Savin de la Saviniere ‡ discussed this finding in 1873. Frugoni,[6] in his book on pulmonary

* References 1 and 3-5.

† References 1, 3, and 4.

‡ Cited by Luisada.[3]

edema,§ devoted considerable attention to infectious edemas. He presented a classification of infectious pulmonary edema as divided into two general types. The first type was considered as secondary infection of the chronic pulmonary edema occurring in patients with cardiac or cardiorenal disease. He thought that this occurred as a result of the "weakening" of the patient because of his basic disease, with localization of the infecting organisms in the lungs.

The second variety was called "true infectious edema," in which the pulmonary edema was present early in the disease and was produced by the specific activity of the etiological agents, even though special mechanical, chemical, or hormonal factors might favor the production of pulmonary edema. This type was further subdivided into (1) satellite infectious edema, the wide area of edema surrounding the nucleus of various kinds of inflammation, and (2) autonomous infectious edema, in which there is no inflammatory nucleus and the edema is the most important manifestation of the pulmonary inflammation. These cases were also called serous pneumonia.

Frugoni recognized that the above scheme of classification was arbitrary and probably too schematic. He pointed out the frequent occurrence of large zones of "satellite" edema in pneumococcal infections in hypertensive and nephrotic patients. Wide zones of satellite edema were also frequent in influenzal pneumonia, where foci of edema alternated with foci of consolidation and where the finding of bubbles of subpleural edema was not unusual. Similar pictures have also been described in streptococcal and typhoidal pneumonias. Inflammatory edema of the lungs has also been described in scarlet fever, chickenpox, German measles, herpes labialis, cholera, anthrax, plague, and acute rheumatic fever.

Of great interest from the clinical standpoint was so-called periphymic edema, the extensive inflammatory edema frequently surrounding small tuberculous foci. The occurrence of multiple small rales frequently leads to the diagnosis of an extensive tuberculous pneumonia while the actual focus is small.

Soma Weiss stated that pulmonary edema localized to an individual lobe could occur and that this took place in a lobe that had previously been damaged by processes like pneumonia || or pulmonary infarction.[7] He believed that one of the best examples of localized pulmonary edema is that occurring in pneumonia. He stressed that this type of edema was produced by gross damage to the pulmonary capillary layers by the bacteria and stated that the high protein content of alveolar fluid indicated the inflammatory nature of the lesion. He pointed out that in some instances of left ventricular failure caused by arterial hypertension attacks of paroxysmal dyspnea are associated with progressive pulmonary engorgement and with progressive histologic changes, such as deposition of fibrin and connective tissue, which in the past had been called "organizing pneumonia." He emphasized that pulmonary edema might be associated with fever and leucocytosis. He also emphasized the difficult roentgenological differential diagnosis between pulmonary edema, pulmonary infarction, pneumonia, fibrosis, tuberculosis, and pneumoconiosis.

Cohn and Steele [8] commented on the frequency of fever during congestive heart failure. In their series of 172 cases of congestive failure, 153 had temperatures of

§ Dr. Aldo Luisada provided a translation of the section of Frugoni's book dealing with infectious pulmonary edema.

|| Personal communication to Dr. M. C. Sosman.

100 F. or higher. One hundred four of these were regarded as due to infection, and 49, as arising from the failure per se. They emphasized the similarity of physical findings in pulmonary infection and in chronic passive congestion and commented on the problem in differential diagnosis that a given case might pose. They proposed an ingenious "rule of thumb" for distinguishing the two, believing that in pulmonary infection the body weight tends to fall and in chronic failure it tends to rise.

Cameron [5] pointed out that in Starling heart-lung preparations contamination of the perfusate with streptococci is a potent factor in initiating pulmonary edema. The pathological lung becomes edematous with great ease when the perfusing pressure is only slightly raised or venous flow is impeded. Reimann ¶ called attention to the interference with self-cleansing processes in lungs involved in pulmonary edema and emphasized infection as an etiological agent in pulmonary edema.

That severe infection may result in shock [10] and that the patient in shock is unusually prone to infections has been repeatedly observed. Moon [11] and Altschule [12] have commented on the frequency of the joint presence of pulmonary edema and shock. The observation of the joint presence of pulmonary edema and shock after acute myocardial infarction is also well known. One of the mechanisms underlying this relationship may be the anoxia of shock. This may lead to changes in pulmonary capillary permeability and thus induce edema. Stead and Ebert [13] have described shock resulting from heart failure. The overactivity of the sympathetic nervous system during bouts of pulmonary edema favors the occurrence of shock. The loss of fluid from the circulation into the edematous lung and from the lung into the environment via coughing favors the development of shock.[12] In our series of cases the presence of two of the members of the triad (pulmonary edema, pneumonia, and shock) made for an unusually high incidence of the third member.

The work of Harford and Hara [14] placed on a sound experimental basis some of the interrelations between pulmonary edema and pneumococcal pneumonia. They utilized mice in which pulmonary edema had been induced by means of three methods: (1) by influenzal virus infection, (2) by the administration of alpha naphthyl thiourea, and (3) by intrabronchial instillation of sterile mouse serum. These mice were subjected to the inhalation of fine droplets containing pneumococci. As controls, mice subjected to the same traumata without the induction of pulmonary edema inhaled the bacteria under exactly similar conditions. This resulted in a greatly increased susceptibility of the mice with pulmonary edema to pneumococcal pneumonia. Their studies also showed that the organisms were able to multiply rapidly in the pulmonary edema fluid.

On the basis of the above, and on the basis of our own illustrative case material to follow, the specific interrelations of pulmonary edema and pneumonia may be listed as follows:

1. Pulmonary edema and pneumonia are frequently found together at postmortem examination. From our hospital records, if one of these entities was present there was approximately 25% chance that the other entity was also noted at postmortem examination.

2. During life a patient may show many of the classic features of one syndrome and at autopsy may be found to have chiefly the other lesion.

¶ Reimann, H., in Cecil.[9]

3. The presence of pneumonia may facilitate the development of pulmonary edema, and the presence of pulmonary edema may facilitate the development of pneumonia.

4. The physical signs and symptoms of these two conditions may be indistinguishable, and even the x-ray findings may not differentiate them.

5. Pneumonia usually starts out as localized pulmonary edema.

6. In the lung tissue adjacent to the area actually involved in pneumonia there is an area of congestion and pulmonary edema.

7. Certain varieties of pneumonic alveolar exudate may be indistinguishable from the transudate of pulmonary edema.

8. In addition to the pulmonary capillary damage produced by the etiological agent in the process of inflammation, there is local interference with oxygenation, producing anoxia, which may be a potent factor in inaugurating pulmonary edema.

9. The systemic effects of pneumonia in terms of anoxia, fever, and intoxication often result in evidence of myocardial abnormality.

10. Not only may the rate of fluid entering the alveoli be increased by pneumonia but also the rate of fluid resorption by the lymphatics may be decreased.

11. Pulmonary edema fluid is an excellent culture medium for organisms.

12. The general status of the patients in acute pulmonary edema is such as to provide excellent conditions for the development of pulmonary infection.

REPORT OF CASES

A. *Pneumonia Masquerading as Pulmonary Edema*

CASE 1 (L. P., 6E477).—A 39-year-old man entered the hospital because of anuria. On admission he was cyanotic and semicomatose, and he had what appeared to be classic pulmonary edema, with distended neck veins and wet rales throughout the lungs. The white cell count was 23,000. The bedside chest film (Fig. 1) showed hazy increased markings prominent in the hilar and perihilar regions, which were interpreted as definite bilateral pulmonary edema. On treatment with digitalis, oxygen, and phlebotomy there was almost complete clearing of the rales and marked improvement in the respiratory state. However, the venous pressure remained elevated. Several hours later the patient suddenly died. On autopsy it was found that there was extensive bilateral confluent bronchopneumonia without any significant degree of pulmonary edema.

Comment.—This case illustrates the occurrence of pneumonia with the clinical manifestations of pulmonary edema.

CASE 2 (R. K., 7E231).—An 18-year-old youth entered the hospital because of oliguria and uremia of one month's duration. He was afebrile, and the chest was clear. The white cell count was 14,000. Admission chest film (Fig. 2 *A*) showed accentuated pulmonary markings with an ill-defined hazy increase in density in the right middle and lower lung field, and this was interpreted as uremic pneumonitis. For two weeks he remained afebrile and appeared to be doing well. On the 17th hospital day he complained of chest pain and developed marked respiratory distress. Medium moist rales were present in both lung fields. A bedside chest film (Fig. 2 *B*) was interpreted as showing massive and extensive pulmonary edema. Despite therapy for pulmonary edema the patient became cyanotic, and frothy sputum was noted at his lips. Postmortem examination revealed extensive pneumonia undoubtedly responsible for the changes noted in Fig. 2 *B* and no significant pulmonary edema.

Fig. 1 (Case 1).—Bedside chest film, showing hazy increased markings prominent in the hilar and perihilar regions.

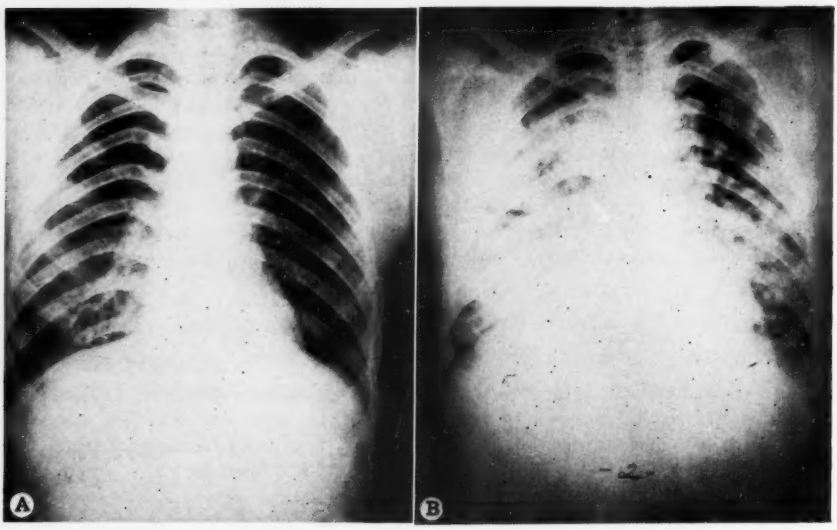

Fig. 2 (Case 2).—*A*, admission chest film. *B*, bedside chest film taken 17 days later.

Comment.—This is an illustration of "silent" pneumonia appearing as acute pulmonary edema.

CASE 3 (W. K., 9A284).—A 55-year-old man with long-standing rheumatic heart disease entered the hospital because of increasing symptoms of congestive heart failure of one year's duration. The neck veins were distended, and the lung fields showed inspiratory wheezes, with slight dullness and moist rales at the left base. The heart was enlarged; there were murmurs of aortic and mitral disease; the liver was felt 3 cm. below the right costal margin, and there was pitting edema of the ankles. By x-rays there was pleural fluid on the right, with an underlying density (Fig. 3). The patient remained afebrile in the hospital and appeared to do well on therapy for congestive failure. On the eighth hospital day he died. At autopsy he was found to have severe bronchopneumonia involving the right middle and left lower lobe, along with much pulmonary edema and congestion. The extent of the pneumonia indicated that it had almost certainly been present on admission and was implicated in the mode of death.

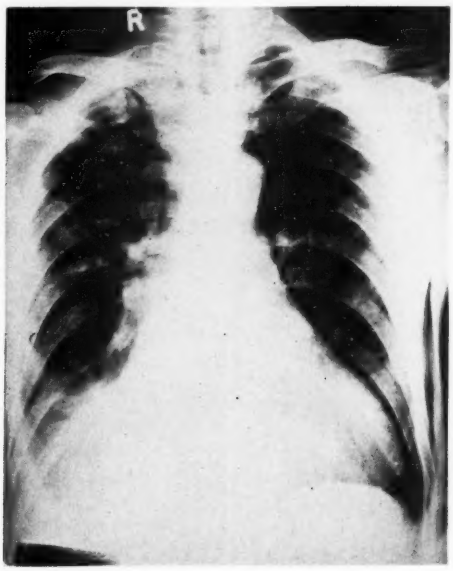

Fig. 3 (Case 3).—X-ray showing pleural fluid on the right, with an underlying density.

CASE 4 (J. F., 7B781).—A 61-year-old man entered the hospital because of congestive heart failure. On physical examination he was afebrile; the lungs were emphysematous, and there was peripheral edema. X-ray of the chest (Fig. 4*A*) revealed emphysematous lungs and some interstitial pulmonary fibrosis. On the 22nd hospital day he developed severe shortness of breath and a picture entirely consistent with acute pulmonary edema. He responded quite well to oxygen and intravenous aminophylline. There was no leucocytosis. A chest film taken at this time (Fig. 4*B*) showed only increased pulmonary congestion. The next day he again developed acute pulmonary edema and died. Postmortem examination revealed extensive bronchopneumonia, which was obviously the cause of death.

Comment.—This is an illustration of "silent" but extensive pneumonia in a patient with pulmonary edema.

B. *Pulmonary Edema Masquarading as Pneumonia*

CASE 5 (T. M., M66699).—A 62-year-old man had had two typical myocardial infarctions with residual angina pectoris. Four weeks before admission he developed substernal pain fol-

lowed by dyspnea and recurrent episodes of pulmonary edema. On admission his temperature was 98.6 F. and his white cell count was 16,000. The admission chest film showed apical tuberculosis and pulmonary congestion. On the second day his temperature rose to 103 F., his white blood cell count rose to 35,000, and dullness and bronchial breathing were noted at the right base. At this time a bedside chest film was interpreted as showing "a marked change, with diffuse consolidation in both bases, more on the left, suggesting bronchopneumonia." He was placed on sulfadiazine, and by the third day the temperature had fallen to normal. A chest film on this day showed "no change in the right lung but a definite spread of the pneumonia in the left lung, which involves the lower two-thirds." On the sixth day a bedside film showed clearing of the pneumonic process at the left base, but there was still consolidation of the lower two-thirds of each lung. The patient developed pulmonary edema on the seventh day and died. Postmortem examination revealed bilateral pulmonary tuberculosis in both apices and extensive pulmonary edema without any bronchopneumonia.

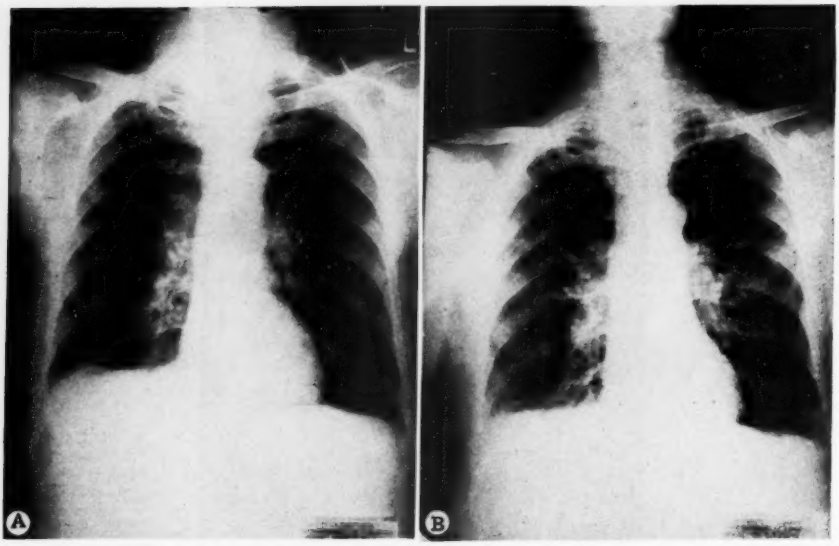

Fig. 4 (Case 4).—*A*, x-ray showing emphysematous lungs and some interstitial pulmonary fibrosis. *B*, x-ray taken on the 22nd hospital day, showing only increased pulmonary congestion.

Comment.—This case illustrates the occurrence of pulmonary edema with fever, leucocytosis, and the x-ray appearance of pneumonia.

C. *Ease of Production of Pulmonary Edema in Patients with Pneumonia*

Case 6 (W. B., 5A221).—A 68-year-old man with known cirrhosis and ascites was found comatose in bed on the morning of admission. The temperature was 100 F. The lungs showed dullness at the bases, with decreased breath sounds at the right base but no rales. The hematocrit reading was 52%, and the serum sodium was 120 mEq. per liter. He was started on antibiotics, and an intravenous infusion of 1,000 cc. of 10% dextrose in water was started. After 500 cc. had been given, the patient developed the signs of acute pulmonary edema. He improved on therapy directed at the pulmonary edema but then went into shock. For six hours before death he presented the picture of pulmonary edema and shock. On postmortem examination the patient showed extensive and diffuse bronchopneumonia with superimposed pulmonary edema. The heart was normal.

Comment.—In addition to demonstrating how easily pulmonary edema may be precipitated in a patient with pneumonia (500 cc. of fluid in a dehydrated patient), this case illustrates the role of low oncotic pressure (serum albumin 1.3 gm. per 100 cc.) in facilitating the formation of pulmonary edema.

CASE 7 (K. N., 8E100).—A 59-year-old man entered the hospital because of a perforated ileum secondary to regional enteritis. Postoperatively, he developed a septicemia with Alcaligenes fecalis. Chemotherapy did not alter the course of the septicemia. He continued to have fever, and the total fluid intake per day was approximately 3,500 cc. On the final day of life he began to hyperventilate and lost consciousness. Coarse tracheal rales and wheezes were noted over all lung fields. He went into shock and died. Postmortem examination showed massive pulmonary edema and some bronchopneumonia. The total lung weight was 2,000 gm.

Comment.—This case illustrates the ease of production of pulmonary edema in a patient with septicemia. It may be considered as the clinical counterpart of the Starling preparation inoculated with Streptococcus, as reported by Cameron.[5]

CASE 8 (E. R., 9A369).—A 45-year-old man was admitted because of cough, chills, fever, and disorientation of two day's duration. It was found that the patient was involved in an overwhelming infection with Diplococcus pneumoniae. Blood, spinal fluid, and nose and throat cultures grew out this organism. On physical examination the entire right chest seemed consolidated, whereas the left chest showed moderate dullness both anteriorly and posteriorly at the bases. There were a few fine rales at the left apex. Postmortem examination showed a massive lobar pneumonia, involving the entire right lung. There was pneumonic involvement of the left lower lobe, and the areas in the left lung not directly involved showed a few red cells and varying amounts of pale eosinophilic fluid filling the alveoli.

Comment.—This is an illustration of pulmonary edema occurring in pulmonary tissue adjacent to pneumonia.

D. *Pulmonary Edema as a Precursor of Pneumonia*

CASE 9 (R. S., 9B340).—A 42-year-old man with rheumatic heart disease was admitted because of advanced congestive failure of several years' duration. He underwent finger fracture valvuloplasty, and shortly after operation he died in ventricular fibrillation. Postmortem examination showed fresh bronchpneumonia and also organizing and organized pneumonia.

Comment.—This case illustrates the role of chronic congestive failure as a suitable substrate for recurrent pneumonia. It is of interest that the pneumonias ranged from old to recent episodes, whereas recurrent pneumonia per se was not a prominent part of the clinical history of this patient. The presence of acute bronchopneumonia in a patient dying in the immediate postoperative period of a totally unrelated cause (ventricular fibrillation) demonstrates the "nonterminal" nature of the bronchopneumonia. It should be stressed that the pneumonic process was present with a flat temperature curve and normal white cell counts.

CASE 10 (W. D., 0D653).—A 63-year-old man entered the hospital because of severe hypertension, uremia, anemia, and dyspnea. He was admitted in pulmonary edema, with inspiratory rales up to the level of the scapulae bilaterally. On bed rest and digitalis most of his moist rales cleared, although he remained severely dyspneic. On the eighth hospital day his temperature was 99.5 F., and on the ninth day it had risen to 101 F. and he experienced a small hemoptysis. Dullness and decreased breath sounds were noted at the left base. This was interpreted as a pulmonary embolus. The patient went steadily downhill and died in shock on the 12th hospital day. Postmortem examination showed extensive pulmonary edema and early pneumonia of both lower lobes.

Comment.—The early pneumonia found in this case probably represents an infection of the pulmonary edema fluid. At this stage the process might have been amenable to antibiotic therapy.

CASE 11 (J. S., A4911).—A 64-year-old man had a history of hypertension and a myocardial infarction. He entered because of progressive symptoms of congestive failure. On admission he was cyanotic, with marked respiratory distress and orthopnea. There were dullness and diminished breath sounds over the lower half of the left chest, and there were rales and rhonchi over the right lower lobe. The white blood cell count was 9,500. An x-ray showed fluid at the left base and vascular congestion. During the patient's first three days in the hospital the temperature ranged around 99.5 F. (rectal). Fluid was removed from the left chest, and the cyanosis disappeared. On the third day the temperature, pulse rate, and respiration rate began to rise; the patient again became cyanotic, and the rales increased. In spite of intensive therapy for congestive failure he went downhill. On the last day bronchopneumonia was suspected and

PATHOLOGIC PHYSIOLOGY OF THE INTERRELATION BETWEEN PULMONARY EDEMA AND PNEUMONIA

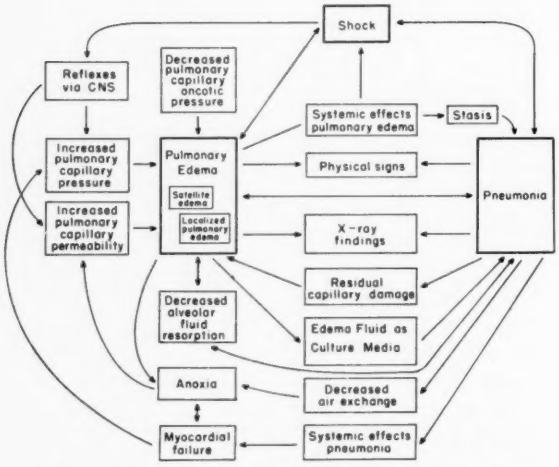

Fig. 5.—Schematic illustration of some of the relationships between pulmonary edema and pneumonia.

penicillin started, but the patient died. Autopsy showed pulmonary congestion in the upper lobes and bilateral bronchopneumonia and pulmonary edema in the lower lobes.

Comment.—This patient illustrates the insidious development of bronchopneumonia in a patient with chronic pulmonary congestion and pulmonary edema. The bronchopneumonia apparently began on the third day, and, if it had been suspected and antibiotic therapy had been given then, the abrupt downhill course might have been altered.

PATHOLOGICAL PHYSIOLOGY

Figure 5 illustrates in schematic form some of the interrelationships that we have already discussed. The four basic factors producing pulmonary edema are listed as increased pulmonary capillary pressure, increased pulmonary capillary permeability, decreased pulmonary capillary oncotic pressure, and decreased alveolar

fluid resorption. Pneumonia acts directly on the pulmonary capillary to increase its permeability and may act indirectly by means of anoxia and myocardial failure. On the other hand, pulmonary edema serves to furnish an excellent culture medium for potentially pathogenic organisms and also immobilizes the patient, decreases his ability to get rid of secretions, decreases ventilatory efficiency, and thus lays the groundwork for pulmonary infection. The mere hospitalization of a patient probably increases the number of pathogenic organisms to which the patient is exposed. The chart also illustrates some of the mechanisms whereby shock may prove a common denominator in establishing the milieu in which both pulmonary edema and pneumonia can occur.

Finally, the chart emphasizes that the physical and x-ray findings are governed by the nature, quantity, and location of the pulmonary edema fluid rather than by the basic mechanisms giving rise to the fluid. This permits pneumonia to masquerade as acute pulmonary edema and vice versa.

THERAPEUTIC AND PROPHYLACTIC IMPLICATIONS

The major therapeutic implications of the concepts presented above fall into two categories:

1. The patient in acute pulmonary edema is exceedingly vulnerable to pulmonary infection. Vigorous chemotherapy would appear to be the best weapon against pulmonary infection, and the earlier this is instituted the greater the probability of success.

2. The patient with established pulmonary infection should be regarded as extremely "fragile" with respect to fluid and osmotic balance at the level of the pulmonary capillary. Parenteral fluids should be given with the knowledge that pulmonary edema can be produced easily. This group of patients should be observed carefully for any signs of the development of pulmonary edema and should be treated accordingly.

SUMMARY AND CONCLUSIONS

Pulmonary edema and pneumonia are closely interrelated.

Both of these conditions frequently coexist, and the occurrence of one predisposes to the development of the other.

The differential diagnosis between these two conditions may be difficult or even impossible to establish by history, physical signs, laboratory study, or x-ray.

The relationship between pulmonary edema and pneumonia stems from their pathophysiological characteristics, which are discussed.

This relationship not only applies to the dying patient but also can occur in patients whose prognosis is good.

Extensive pneumonia may exist in a patient in a completely silent form without clinical or x-ray evidence. It may be an important contributing cause of sudden death.

Prophylactic chemotherapy is indicated in the routine management of the patient in acute pulmonary edema.

The treatment of the patient with pneumonia should include acute awareness of the possibility of pulmonary edema.

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MARROW IRON STORES IN ANEMIA

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WITH THE renewed interest in iron metabolism that has been stimulated by the increased availability of serum iron levels, radioactive iron studies, and bone marrow iron stores estimation, we have undertaken a study of bone marrow iron stores measured qualitatively, as reported by Rath and Finch.[1]

Masshoff and Gruner [2] have been unable to confirm the reciprocal relationship between circulating hemoglobin and iron stores demonstrated by Rath and Finch; however, Davidson and Jennison [3] have reported a similar study, using bone marrow tissue sections and fragment smears, confirming the observations of Rath and Finch, except in the miscellaneous group, which includes the leukemias.

METHOD

We have used smears of bone marrow fragments in our study and have correlated the iron stores with the circulating hemoglobin level and with the type of anemia present.

The materials used in this study were 128 sternal and, occasionally, iliac bone marrow samples, of which the first 90 were consecutive and not from selected cases. The last 38 were from selected cases, to give more variance to the group as to types of anemias studied and to aid in follow-up to evaluate results of therapy. There were 12 patients from whom inadequate marrow fragments were obtained and for whom no evaluation of iron stores was made. Thus, 116 marrow samples were studied, from patients with various diseases (Table 1).

All marrow samples were fixed and stained in groups with 20% potassium ferrocyanide and concentrated HCl, as suggested by Rath and Finch. The first 75 were identified by number only and were graded independently by us without knowledge of the patient's disease. The grading varied from 0 to 4+. A trace represents essentially no stainable hemosiderin. One plus is decreased, a slight amount; 2+ is moderate and is considered normal; 3+ is increased and is moderately heavy, and 4+ is very heavy. At least two fragments were examined from each marrow sample.

RESULTS

The results are placed in several categories: iron stores from patients with no anemia, with a normocytic anemia, with a microcytic anemia, with a macrocytic anemia, in pregnancy, and with polycythemia. The categories of no anemia and normocytic anemia are divided into marrow-replacement diseases, hemolytic diseases, acute bleeding, and miscellaneous diseases. These groups are presented in Table 1.

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No anemia is diagnosed if the hemoglobin is more than 12 gm. and the red blood cell count is over 4,000,000 per cubic centimeter. Normocytic anemia includes patients with less than 12 gm. of hemoglobin, fewer than 4,000,000 red cells per cubic centimeter, a color index between 0.8 and 1.0, mean corpuscular hemoglobin

TABLE 1.—*Conditions Studied for Marrow Iron Stores*

	Cases, No.
Diseases with normocytic anemia or no anemia	
Marrow replacement	
Leukemia	19
Hemolytic disease	
Congenital hemolytic anemia	3
Acquired hemolytic anemia	2
Acute bleeding	4
Miscellaneous	
Chronic infections	14
Hodgkin's disease and lymphosarcoma	6
Rheumatoid arthritis	5
Carcinoma	7
Collagen disease	5
Nephritis	5
Chronic refracting anemia	3
Congenital atresia of bile ducts	1
Agnogenic myeloid metaplasia	1
No disease	2
Diseases with microcytic anemia	
Chronic bleeding	7
Nutritional deficiency	5
Familial hereditary hypochromic anemia	1
Diseases with macrocytic anemia	
Pernicious anemia	7
Cirrhosis	4
Polycythemia	4
Pregnancy	11
Total	116

TABLE 2.—*Iron Stores with No Anemia, Twenty Marrow Samples*

	Iron Stores				
	4+	3+	2+	1+	Trace
Marrow replacement	1	1	1	0	0
Hemolytic anemias	0	0	1	0	0
Acute bleeding	0	0	0	2	1
Miscellaneous	3	1	7	0	0
No disease	0	0	2	0	0
Total	4	2	11	2	1

of 27 to 31 $\mu\gamma$, mean corpuscular volume of 82 to 92 cu. μ, normal mean corpuscular hemoglobin concentration, and morphologically normocytic and normochromic red cells. The classification of microcytic anemias includes patients with a hemoglobin of less than 12 gm., a color index of less than 0.8, a mean corpuscular hemoglobin of less than 27$\mu\gamma$, a mean corpuscular volume of less than 70 cu. μ, and microcytosis and hypochromia, with or without poikilocytosis and anisocytosis demonstrated in the blood smear. The classification of macrocytic anemia is based

on the usual criteria, including a megaloblastic bone marrow, except in patients with cirrhosis, in which cases examination of the peripheral smear is used and the presence of moderate numbers of macrocytes without megaloblastic bone marrow is accepted.

In the group with no anemia, there were four patients with 4 + iron stores (Table 2). Two of these had long-standing chronic infections; one was a patient with subacute bacterial endocarditis and the other had chronic lymphatic leukemia.

TABLE 3.—*Iron Stores in Normocytic Anemias, Fifty-Seven Marrow Samples*

	Iron Stores				
	4+	3+	2+	1+	Trace
Marrow replacement	8	7	1	0	0
Hemolytic anemias	0	3	1	0	0
Acute bleeding	0	0	0	0	1
Miscellaneous	6	16	10	3	1
Total	14	26	12	3	2

TABLE 4.—*Iron Stores in Macrocytic Anemia, Eleven Marrow Samples*

	Iron Stores				
	4+	3+	2+	1+	Trace
Pernicious anemia					
Before therapy	2	3	0	0	0
After therapy	0	1	1	0	0
Cirrhosis (4 patients)	1	1	2	0	0
Total	3	5	3	0	0

TABLE 5.—*Iron Stores in Microcytic Anemia, Thirteen Marrow Samples*

	Iron Stores				
	4+	3+	2+	1+	Trace
Chronic bleeding	0	0	1	1	5
Nutritional iron deficiency					
Child	0	0	0	1	3
Adult	0	0	0	1	0
Familial hereditary hypochromic anemia	0	1	0	0	0
Total	0	1	1	3	8

Of the three patients with decreased iron stores, two had idiopathic thrombocytopenic purpura with numerous epistaxes. The other was a man whose condition had been diagnosed as polycythemia vera elsewhere and who had had 1,000 cc. of blood removed recently. We were unable to confirm the diagnosis. The iron stores of the remainder of the patients did not vary far from normal.

Table 3 refers to iron stores in patients with normocytic anemia of varying degree. The general trend is for increased iron stores in normocytic anemias, except in those with acute bleeding. One patient with a trace of iron was still anemic after hemorrhage from a duodenal ulcer and gastrectomy. The anemia was normocytic, and there were reduced iron stores. Two of the four patients in the miscellaneous category had additional reasons for their reduced iron stores; one was only

three months old, and the other had a marked general nutritional deficiency. There was no clear-cut relationship, however, between the degree of anemia and the amount of iron stores in these cases.

The iron stores in macrocytic anemias, in five patients with untreated pernicious anemia, were increased. Eight weeks after treatment with vitamin B_{12}, a repeat marrow examination in two patients showed some reduction in the iron stores. In four patients with cirrhosis of the liver there was some increase in the iron stores (Table 4).

The iron stores in microcytic anemia were reduced in nearly all patients (Table 5). One patient with Hodgkin's disease and bleeding had normal iron stores, and one patient with familial hereditary hypochromic anemia had increased iron stores.

The iron stores were measured in 11 patients during pregnancy (Table 6). This is an inadequate number from which to draw any conclusions; however, there appeared to be a tendency for the iron to be decreased as the hemoglobin level decreased.

Two patients with polycythemia vera were studied before and after therapy with triethylene melamine without phlebotomy. The iron stores were a trace and 1 + prior to treatment, and with the fall in hemoglobin to normal levels the iron stores rose to normal levels.

TABLE 6.—*Iron Stores in Pregnancy, Eleven Marrow Samples*

Hemoglobin level	Iron Stores				
	4+	3+	2+	1+	Trace
Over 12 gm.	0	0	2	0	0
10.5 to 12 gm.	0	0	1	1	0
Under 10.5 gm.	0	1	1	5	0
Total	0	1	4	6	0

COMMENT

The iron that we measured was probably hemosiderin, although, as Finch and co-workers [4] have pointed out, ferritin may also give a positive Prussian blue reaction with potassium ferrocyanide, but it is not visible as particulate matter. Although it cannot be stated for certain that marrow hemosiderin is a fair estimate of total body iron stores, we have done splenic aspirations on three of the patients and, on one occasion, a liver biopsy, in which instances the amount of iron stores in each patient was comparable for all sites at the same time. It is being recognized that iron stores in the liver increase with anemia and cirrhosis of the liver. This would appear to be similar to our findings in the bone marrow.

In our two cases of polycythemia vera, as the hemoglobin increased to 20 to 25% above normal the iron stores tended to disappear. With a reduction in circulating hemoglobin to normal levels, the iron stores returned to normal. The patient who had had 1,000 cc. of blood removed for suspected polycythemia vera had a normal hemoglobin value and decreased iron stores. This represented approximately 20% removal of body iron. These two situations conform with the idea that 20% of total body iron is in iron stores and is readily available for formation of hemoglobin.

One other patient with a chronic refractory anemia, who had a hypercellular marrow which had responded to no antianemia therapy, had his iron stores graded

both before and after splenectomy. This operation was done because of minimal evidence of hemolysis and resulted in slight improvement. In spite of less frequent and less numerous transfusions, his iron stores rose from 3 + to 4 +. Actually, this 4+ represented the greatest amount of iron that was present in any of our marrow samples. Apparently, this patient lost a location for iron stores and began greater accumulation of iron in other areas, such as bone marrow.

A difference was noticed also in the way in which iron accumulates. In chronic infections or diseases of long standing the iron store was slightly greater than in leukemias and hemolytic diseases in general. However, the most striking difference was in the clumping of iron in chronic infections, whereas in the leukemias, particularly acute leukemias, when the anemia was of recent onset, the iron was in fine droplets and was diffusely scattered throughout the marrow-fragment area. This was best seen with oil immersion. It might be that in tissue sections it does not show up as well, and this might account for the difference between our results and those of Davidson and Jennison in this group of diseases.

There have been five reports in the recent literature, which, with our patients, include the evaluation of iron stores in more than 985 marrow samples. Our findings agree primarily with those of Rath and Finch,[1] Stevens and co-workers,[5] and Hutchison,[6] in that all patients with chronic bleeding or nutritional anemia, primarily that of infants, have decreased to absent marrow iron stores. Those with hemolytic disease, marrow-replacement disease, and the miscellaneous group of diseases have normal to increased iron stores. Stevens and co-workers [5] and Hutchison [6] have also commented upon the characteristic clumping of iron stores that occurs in chronic infection, that we have noted. Increased iron stores with clumping were present in four of the five patients with rheumatoid arthritis.

The determination of iron stores is relatively simple and can be done by anyone doing marrow aspirations. The grading or estimation of the hemosiderin content of the fragment in a general way is not difficult, particularly if one only judges by reduced, normal, or increased iron stores and if one is looking at the marrow fragment area and not at a smear, with peripheral blood dilution. It is of value in the diagnosis of anemia of undetermined origin, particularly anemia due to the group of chronic infections; in the diagnosis of hemosiderosis, and in the diagnosis of hereditary leptocytosis (Mediterranean anemia, trait, or disease). It should be determined in any microcytic type of anemia, when there is any uncertainty as to whether there is actual iron loss, and, when serum iron determinations are unavailable, before massive doses of iron preparations are used orally or intravenously. The danger of toxicity of iron therapy has recently been pointed out,[7] and the degree of toxicity has been related to the serum levels reached. If the iron stores are increased, in many cases the serum iron level is elevated, and this would suggest that the anemia is not caused by iron deficiency.

SUMMARY

One hundred sixteen marrow samples were studies for hemosiderin and graded qualitatively. The iron stores and the type and degree of anemia have been correlated. There are increased iron stores in the macrocytic anemias and in normocytic anemias not due to acute bleeding. This is noted particularly in patients with

chronic infection. The iron stores are reduced in patients with chronic bleeding and nutritional anemias of infancy. In pregnancy the hemoglobin level is possibly related to the reduction in iron stores.

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SICCA SYNDROME

Gougerot-Sjögren Disease

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THE SYMPTOM complex of dryness of the eyes and mucous membranes with enlargement of the parotid glands in menopausal women was described by Henri Gougerot in 1925 [1] and has been the subject of numerous studies reported by the Swedish ophthalmologist, Henrik Sjögren (1933-1952).* Frequent references to Sjögren's disease, Gougerot's disease, and Sjögren-Gougerot or Gougerot-Sjögren disease and/or syndrome appear in European medical literature; such reports are rare in American medical journals at the time of writing and are confined chiefly to the field of ophthalmology.† There is good reason to believe that this syndrome is a manifestation of a systemic disease. Keratoconjunctivitis sicca, rhinitis sicca, pharyngitis sicca, xerostomia, and swelling of the parotid glands are cardinal features. In addition, rheumatoid arthritis, dental caries, accelerated sedimentation rate, achylia gastrica, diminished perspiration, dryness of the vulva and vagina, altered glucose-tolerance curve, hypochromic anemia, alopecia, Raynaud phenomena and scleroderma have been described.[18]

The association of such a wide variety of manifestations with keratoconjunctivitis sicca may at first appear coincidental; however, their frequency in groups of cases reported by different observers in various countries precludes mere coincidence as the explanation. It is more probable that the several manifestations have in common some disturbance of system or mechanism or both.

The syndrome rests upon a rather slender basis in pathologic anatomy. Material obtained by biopsy of the orbital and palpebral lacrimal glands; conjunctiva and cornea; parotid, sublingual, and labial salivary glands; nasal and laryngeal mucosae; skin, and vaginal mucosa has been studied.‡ The findings led Sjögren to the conclusion that degeneration of the glandular parenchyma is primary and constitutes the basic anatomic feature of the disease. Several cases with necropsy have been reported.§ A detailed study of the findings at necropsy in one of these cases was carried out by Dorothy Russell.‖ She concluded that "The selective inflammatory

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This study was aided by a contribution from the Aaron W. Davis Fund.

* References 2-11.

† References 12-17.

‡ References 2-7, 17, and 19.

§ References 14 and 20-22.

‖ Cited by Ellman and others.[20]

involvement, with degeneration and atrophy, of the salivary and lacrimal glands, of the submucous glands throughout the respiratory and upper alimentary tract including the esophagus, and of the sweat glands of the skin, suggests a unique disease."

Up to the present, attention has been focused chiefly upon the keratoconjunctivitis sicca,[23] and the major contributions have been made by ophthalmologists. However, it has become evident that the extraocular manifestations of this disease are equally important, and it is likely that internists will become increasingly aware of this syndrome. Sjögren has used the term "sicca syndrome" to stress the outstanding clinical symptoms, as well as the descriptive term "dacryosialo-adenopathia atrophicans." Since a descriptive term for a disease with such protean manifestations is not practical, it is simpler for the present to use the term "sicca syndrome" or the dionym of the two men who established the entity.[24]

In many of the cases thus far reported, enlargement of the parotid glands is present in addition to keratoconjunctivitis sicca. Other salivary glands are frequently involved as well and may show changes in size and consistency without clinical evidences of inflammation. It is noteworthy that the lacrimal glands, though regularly affected, are rarely palpable. Burning and dryness of the eyes occur with concomitant diminished or absent formation of tears. This feature can be demonstrated by means of Shirmer's test.¶ With the Rose-Bengal test, characteristic triangular staining on each side of the cornea in the area of the palpebral fissure is observed.[10] Dryness of the lips may be noticed long before the development of dryness of the mouth. The mucous glands of the mouth, nasopharynx, and respiratory tract are sometimes affected and become atrophic. The sweat glands of the skin and acid-secreting glands of the stomach have also been involved in some cases. However, it is the dryness of the eyes and mouth which disturbs the patients most, and it is the atrophy of the mucous glands of the tracheobronchial mucosa which leads to the most severe complication, namely, pulmonary infection.[25]

Differential diagnosis may be difficult. Mikulicz's disease, uveoparotitis (Heerfordt) of sarcoidosis, lymphomas, and mumps must be considered.[8] The recognition of this syndrome has reopened the question of the nature and meaning of Mikulicz's disease as well as other considerations regarding the physiology, pathology, and interrelationships of the lacrimal, salivary, sweat, bronchial, and other eccrine glands.[26]

The entire concept has been challenged recently in an elaborate monograph by Stig Holm.[27] In view of the obvious importance of this subject to internal medicine and the paucity of data regarding the pathologic anatomy, the following case is reported.

REPORT OF A CASE

R. E. is a 49-year-old white woman (clinical record as of May 18, 1952).

Family History.—Mother died of carcinoma of liver at 55. No other chronic diseases recorded in the family.

Previous History.—Scarlet fever in childhood; no complications or sequelae. 1933, severe arthritis of both hands with generalized muscular aches. This was said to have followed an attack of tonsillitis. Considerable clinical improvement followed tonsillectomy at this time. 1934, bilateral otitis media following upper respiratory infection. Recovery after conservative therapy.

¶ Cited by MacLean.[16]

1940, chest pain along lower costal margins and dorsal spine. March, 1949, arthritis in both knees, with redness, tenderness, limitation of motion, and evidences of effusion. October, 1949, menopause completed. Severe dental caries with loss of teeth during past three years.

Present Illness.—During the spring and summer of 1951 the patient had noted dryness of the lips and mouth; this dryness was more marked in the lips and was accompanied by excoriations of the skin around the mouth. Additional symptoms were sensations of burning and dryness of the eyes, with inability to make tears. The latter symptom had been treated with artificial tears two years ago. The sensation of dryness of the mouth involved the tongue and pharynx and was accompanied by a change in taste sensation, manifested by an inability to distinguish flavors in a fashion which had been normal in this patient prior to the onset of these symptoms. In addition, she became intolerant to acid-containing foods, such as fresh fruit, and also to salty or highly seasoned foods because they produced burning sensations of the mouth and tongue. The patient states that for several months she has noted numbness and "pins and needles" in the second, third, and fourth fingers of the right hand after exposing it to cold air or cold water.

She has lost about 20 lb. (9 kg.) and attributes this loss to difficulty in eating because of the gingival soreness and dryness of the mouth. She noted recently tender gums, dental caries, and beginning loss of teeth.

The patient was seen by a dermatologist for the dryness of the mouth and cutaneous excoriations about the lips. He made no definite diagnosis. She was given intensive oral and intramuscular vitamin therapy without benefit. Another dermatologist administered low-voltage x-ray treatment to the perioral lesions, with slight benefit. However, the dryness and burning of the mouth persisted. She was also seen by an ophthalmologist, who prescribed artificial tears. The lacrimal glands could not be palpated. Sweating was normal. Several blood cell counts during this period of observation gave normal results.

In March, 1952, while the patient was on a visit to Puerto Rico, swelling in both preauricular regions was noted, unaccompanied by pain or tenderness. On examination, after her return to New York, a bilateral irregular enlargement of the parotid glands was observed. The consistency of the glands was within normal limits. The mouths of Stenson's ducts appeared normal. The submaxillary glands did not appear to be involved, but the right sublingual gland could be palpated and seemed enlarged. There was no generalized or local lymphadenopathy. General physical examination and x-ray of the chest and small bones of the hands and feet were negative. Laboratory findings were within normal limits. There was no fever or cough at any time. The appetite was good; intestinal function was normal.

On May 18, 1952, the patient was admitted to Lebanon Hospital (L. H. Admission 44870) for further study. The following laboratory data were obtained: Blood Wassermann test was negative; blood cell count, normal; urine, normal; sedimentation rate, 13 mm. in an hour (Westergren); thymol turbidity, less than 5 units; gamma globulin, 7 (Kunkel) units; total protein, 6.6 gm., serum albumin, 3.6 gm., and serum globulin, 3 gm. per 100 cc.; roentgenogram of chest, normal; sternal marrow, normal. On May 23, 1952, biopsy of the left parotid gland was performed under general anesthesia.

Clinical Course.—The patient has been under treatment with cortisone since June, 1952, with marked regression of the swelling of the parotid glands, diminution in dryness of the mouth and, to a lesser degree, of the eyes. She has not developed any tracheal or bronchial symptoms, and her appetite remains good. The right sublingual gland can no longer be palpated. She has gained in weight (March, 1952, 121 lb. [54.5 kg.]; July, 1953, 136 lb. [61.2 kg.]). Her general appearance has improved, and her skin is supple and of normal consistency. On July 14, 1953, the hemoglobin was 13.6 gm. and the red cell count was 4,750,000. There is no adenopathy. The liver and spleen cannot be palpated. There are minimal arthritic changes in both hands. The "Raynaud phenomena" persists, and there is continuing dental caries with loss of teeth, but at a slower pace than at the onset of her illness.

The dosage of cortisone, which had been started at 100 mg. daily, has been reduced to 25 mg. daily, in two doses. One or two days are skipped occasionally.

Report of Histopathologic Findings.#—Sections of the small fragment of parotid gland reveal a more or less uniform alteration in all fields. The secreting parenchyma is almost totally absent. Only the ducts remain; the intervening space is occupied by a mononuclear infiltrate which is compact in some areas, looser in others, and supported by connective and vascular tissues. The lobular architecture of the gland is undisturbed, and while the interlobular septa contain a few mononuclear cells here and there (Fig. 1) they appear essentially to be uninvolved by the process which has so strikingly altered the glandular parenchyma. The capsule of the parotid gland does not appear in these sections. Scattered fat cells can still be recognized within the lobules.

Many of the cells comprising the infiltrate are lymphocytes (Fig. 2). These are either diffusely scattered in the interstitium or arranged in compact nodular aggregates, occasionally with germinal centers. Plasma cells are present in fair numbers (Fig. 3); there are also occasional polymorphonuclear leucocytes and very infrequent eosinophiles; a rare Russell body can be

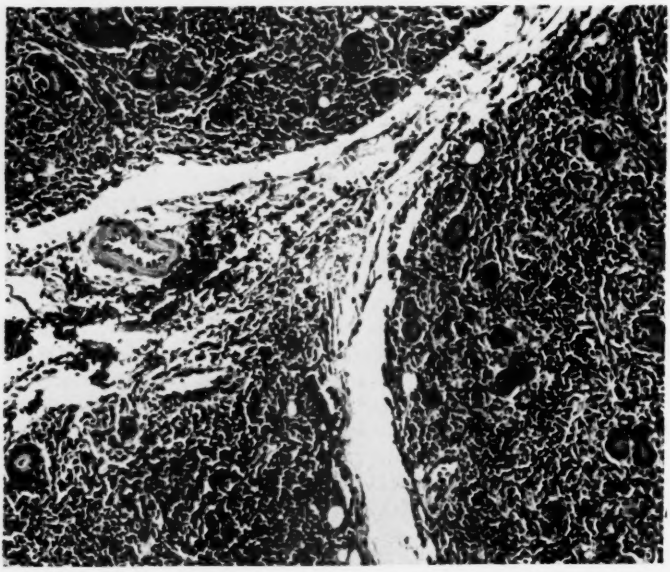

Fig. 1.—Parotid gland. Average low-power field, showing disappearance of terminal secreting portion. Infiltrate present chiefly within the lobules, with relatively scanty involvement of the septa; × 210.

observed. The duct system of the paratoid gland appears to be intact throughout, including the terminal branching portions. Many of the finest branches enclose pink-staining amorphous material; larger branches occasionally contain clusters of polymorphonuclear leucocytes.

An unusual appearance is produced by circumscribed nests of cells in reticular arrangement, which appear to compress many small ducts by external pressure. These cells, whose morphology does not permit certain identification, are located between the basement membrane and the epithelial lining cells of the ducts. In cross section, the cell nests, eccentrically displaced duct lining cells, and the duct sheath may have a "signet ring" appearance (Fig. 4). In longitudinal sections, irregular groups and clusters of these cells intermingled with compressed groups of the lining cells of the ducts may produce bizarre patterns, some of which resemble the nests of "epimyoepithelial cells" illustrated by Morgan and Castleman [26] (their Figure 13).

Lebanon Hospital Surgical Pathology No. 21578, May 23, 1952.

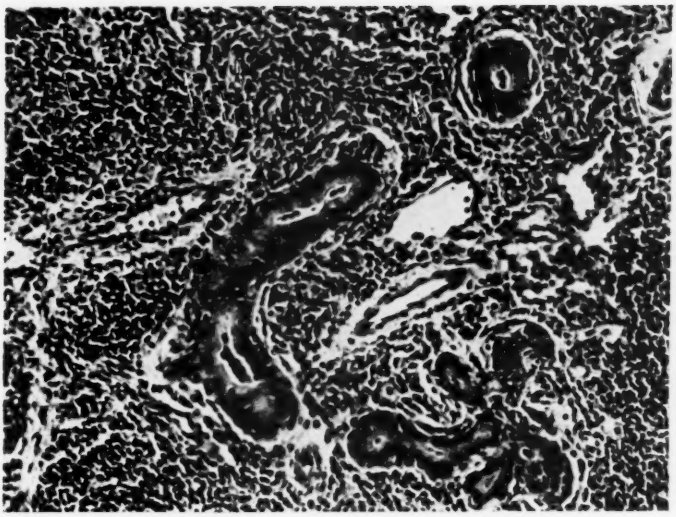

Fig. 2.—Parotid gland. Average medium-power field, showing total disappearance of terminal secreting portion. Residual salivary ducts, corresponding probably to striated and intercalated portions. Dense infiltrate consisting chiefly of lymphocytes and plasma cells; × 320.

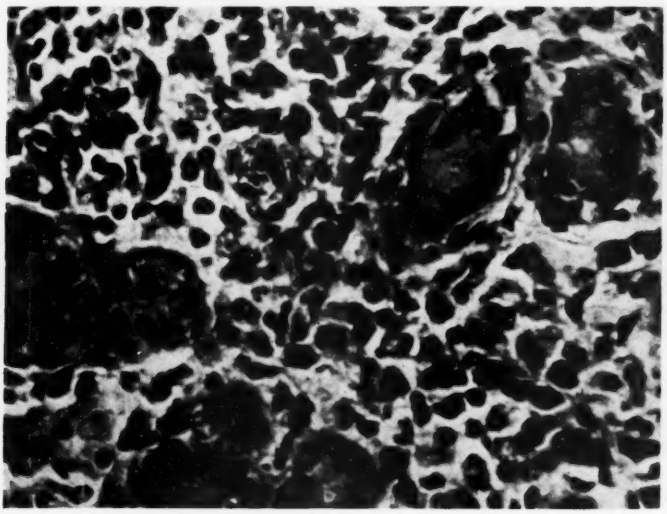

Fig. 3.—Parotid gland. Average high-power field, showing absence of normal secreting portion. Small ductules corresponding probably to necks of isthmic portions. Details of an area of infiltrate in which plasma cells predominate; × 760.

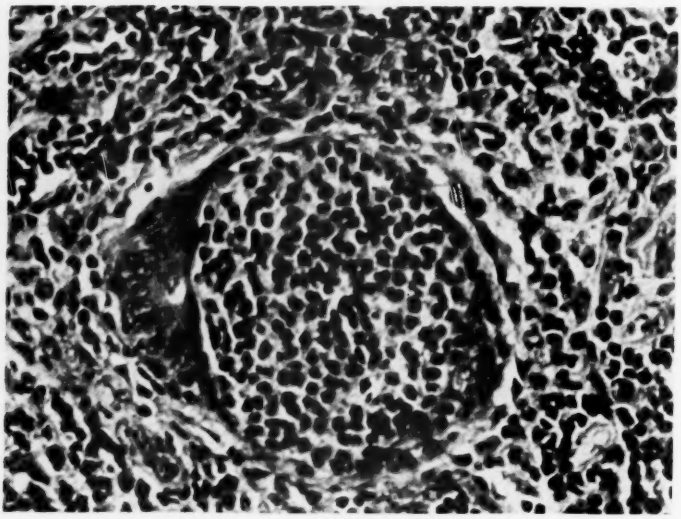

Fig. 4.—Parotid gland. Salivary duct altered by a nest of cells between the basement membrane and epithelial lining cells; marked eccentric displacement and crescentric distortion of the epithelium. These cells may be of myoepithelial origin; × 700.

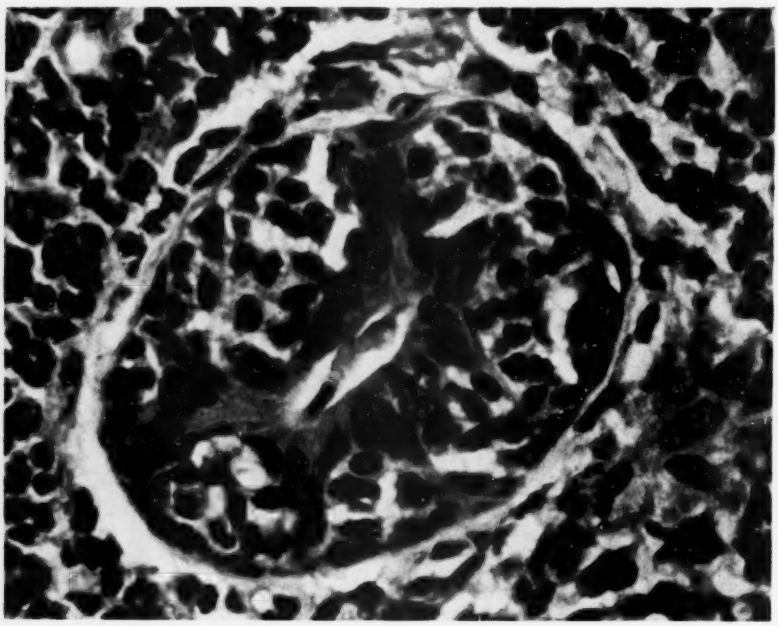

Fig. 5.—Parotid gland. High-power photomicrograph showing detailed morphology of nests of large cells in reticular arrangement between basement membrane and epithelial lining cells of salivary gland ductule. The lumen of the ductule is reduced to a narrow slit by external compression and contains amorphous pink-staining material and a pyknotic nucleus; × 1,600.

With the oil-immersion objective, these cells appear as polygonal elements with interconnecting cytoplasmic processes. There are multiple indentations of the nuclear membranes; the intranuclear space contains abundant threads of chromatin and one or more tiny round blue-staining granules. The cytoplasm is scanty in amount, pale pink in sections stained with hematoxylin and eosin, and very faintly reticulated in character. The location and cytologic characteristics of these cells suggests myoepithelial origin (Fig. 5).

Mitotic figures are rare in the "myoepithelial" cells but can be found easily in the germinal centers of nodular aggregates of lymphocytes. Inclusion bodies could not be found.

COMMENT

The clinical diagnosis of sicca syndrome in our case is based upon the occurrence of keratoconjunctivitis sicca, with dryness of the mucous membranes and bilateral enlargement of the parotid glands, in a middle-aged, menopausal woman. The association with rheumatoid polyarthritis, Raynaud phenomena, and severe dental caries is characteristic.

The mixed composition of the cellular infiltrate and the almost complete absence of involvement of the interlobular septa suggest a non-neoplastic origin of the infiltrate in the specimen obtained from the parotid gland. The atrophy and disappearance of the secretory portion of the parenchyma with replacement fibrosis further support this interpretation. The clinical course and histopathologic findings argue against neoplasm, although this possibility cannot be ruled out entirely as yet, in view of the complete lack of experience with the ductal changes encountered.

The nests of cells in reticular arrangement in the region between the epithelium and basement membrane of the salivary ducts (Fig. 5) have not been described previously. The nature and significance of these cells can be elucidated only by the study of additional material. A relationship to the "epimyoepithelial islands" described by Morgan and Castleman [26] is possible. Similar patterns appear in the illustrations of the papers by Lutman and Favata [13] (their Figure 3, Case 2), and by Morgan and Raven [18] (their Figure 191, Case 2). Sjögren and Ellman, Weber, and Goodier* do not describe such alterations in their histological reports.† The question of whether this peculiar cellular proliferation may be primary, with resultant gradual obliteration of the ducts and secondary parenchymal atrophy, should be investigated. A more objective basis for the identification of these cells as to origin should be sought with special histological techniques and comparative anatomical studies. Patterns of this type were not encountered by Radnót in her study of the orbital lacrimal glands obtained at 500 routine necropsies.[28] A similar study of salivary glands is not available.

The proper status of Gougerot-Sjögren disease with respect to Mikulicz's disease is unclear. Morgan and Castleman [26] have recently redefined Mikulicz's disease as a benign chronic condition, predominantly of women of the fifth and sixth decades, which almost always involves one or more salivary glands and less often involves the lacrimal glands. Grossly, there is preservation of the normal architecture, with diffuse enlargement; microscopically, there is replacement of the acinar parenchyma by lymphoid tissue and an intraductal proliferation of epithelial and myoepithelial

* References 20 and 25.

† A paper by Grignolo (Bull. oculist. **24**:347, 1945) was not available.

cells. The similarity of the disease thus characterized to Gougerot-Sjögren disease is so striking that these authors have undertaken a reinvestigation of their entire material to explore further the interrelationship of the two.

Morgan and Raven [18] state that Gougerot-Sjögren disease never causes swelling of the lacrimal glands, whereas in Mikulicz's disease this is regularly present. That this distinction is not basic is evident from the fact that the lacrimal glands in Gougerot-Sjögren disease, though not enlarged, are severely affected; on the other hand, Morgan and Castleman found that the lacrimal glands were not involved as frequently as the salivary glands in their cases of Mikulicz's disease. Unfortunately, specimens of lacrimal gland for histological examination were available in only 1 of their 18 cases.

The sicca syndrome occurs predominantly in middle-aged women; 15 of Morgan and Castleman's 18 patients with Mikulicz's disease were also middle-aged women. Despite conflicting reports, it appears to be established that atrophy and disappearance of secreting parenchyma occurs in both Mikulicz's and Gougerot-Sjögren disease, and it should not be surprising, therefore, if clinical evidence of loss of secretion is also shared by them. Several authors have suspected cross diagnosis of the two conditions.[20] Whether or not the extraocular manifestations now known to be associated with keratoconjunctivitis sicca may also occur with significant frequency in Mikulicz's disease must await further analysis of clinical data.

No attempt will be made in this report to review completely the extensive literature on the subject of keratoconjunctivitis sicca and the sicca syndrome. There are more than 250 references in the review by Stig Holm [27]; other excellent reviews are those by Henderson [12] and Touraine.[29]

The clinical disturbances which have been reported to accompany the sicca syndrome include achylia gastrica, dryness of the tracheobronchial mucosa, dryness of the vulva and vagina, diminished perspiration,‡ rheumatoid arthritis,§ dental caries, accelerated sedimentation rate, hypochromic anemia, altered glucose-tolerance curve, alopecia, Raynaud phenomena,‖ Felty's syndrome,[33] and scleroderma.¶ Also mentioned are dysphagia of the Plummer-Vinson type,# acrocyanosis, aphonia, delusional mental changes,* pigmentation of the legs,† hypothyroidism,[40] premature senility,‡ ozena,§ telangiectasis of the lips and finger tips,[25] granuloma annulare,[17] and generalized necrotizing arteritis.[22] The literature contains numerous etiological speculations regarding the possible roles of avitaminosis,‖ hormonal imbalance,[18] neuroendocrine functional disorders,[27] hypersensitivity,¶ chronic infection, and congenital and familial factors.#

‡ References 18, 20, and 25.
§ References 9, 21, 30, and 31.
‖ References 25 and 32.
¶ References 9, 31, and 34-36.
# References 25, 32, and 37-39.
* References 25 and 36.
† References 35 and 36.
‡ References 9, 31, and 34.
§ References 4, 20, and 36.
‖ References 17, 18, 32, 37, and 38.
¶ References 15 and 16.
# References 11, 14, and 41.

Many therapeutic approaches have been tried. Treatment with cortisone and corticotropin has been carried out in several cases, and clinical improvement was striking in a few.* In our case, cortisone has been administered more or less continuously since June, 1952. The swelling of the parotid glands has regressed, but some palpable enlargement persists. The dryness of the mouth has abated, and there has been improvement in the appetite, with a gain in weight, but the patient is still unable to make tears. Attempts have been made to treat the keratoconjunctivitis sicca by the direct installation of cortisone into the conjunctival sac †; results in our patient were not favorable.

SUMMARY

A case of sicca syndrome in a menopausal woman, aged 49, is reported. The clinical manifestations included keratoconjunctivitis sicca, dryness of the mucous membranes, bilateral enlargement of the parotid glands, rheumatoid arthritis, severe dental caries, and Raynaud phenomena.

A detailed report of the histopathological findings in a specimen obtained by biopsy of the parotid gland is presented. Previously undescribed nests of cells in reticular arrangement between the lining epithelium and basement membrane of the ducts were observed. These cells may be of myoepithelial origin, and their proliferation may be causally related to the atrophy of the secreting portion.

The importance of the sicca syndrome to internal medicine and pathology is emphasized.

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Progress in Internal Medicine

SYPHILIS

Review of the Recent Literature

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(Concluded from Page 628)

PROPHYLAXIS

THAT PROGRESS in the field of prophylaxis of syphilis is being made is indicated by two pertinent recent publications. In an editorial in the *American Journal of Syphilis, Gonorrhea and Venereal Diseases* [230] concerning oral administration of penicillin in the prophylaxis of syphilis, the editor points out that while a single penicillin tablet ingested soon after exposure has been demonstrated to be highly effective in the prevention of gonorrhea and has been widely used in the Navy for this purpose such a method is not effective in the prophylaxis of syphilis. Weinstein and his co-workers [253] have shown that 6,750,000 units of penicillin, administered by mouth, in conjunction with fever, is ineffective treatment for primary and secondary syphilis. Much less treatment is need to cure syphilis in the early incubation period. It is estimated that an amount of penicillin sufficient to provide blood penicillin levels of 0.2 γ per milliliter for a period of 8 to 24 hours might suffice. However, no oral preparation of pencillin will provide this concentration and duration of penicillin level after a single dose. Until a new and more effective penicillin preparation becomes available, penicillin prophylaxis of syphilis by mouth is not feasible and should not be attempted. Because the sulfonamides have proven ineffectual, there has been reluctance to undertake large-scale programs with penicillin or other useful antimicrobial agents. The report of the Navy's experience [231] over a period of three years with the oral use of pencillin as a prophylaxis of gonorrhea is therefore of considerable interest to the student of syphilology. The efficacy of this procedure has remained unchanged after three years, and resistant strains of gonococci have not been encountered. It is considered extremely improbable that this method of administration will have any influence on the development of resistant forms of either the gonococcus or of Treponema pallidum. The data from the Navy suggest that doses of 250,000 units of penicillin by mouth may also prevent syphilis, but this is not dependable and will almost certainly fail if the victim receives a heavy inoculum. There has been no indication of altering or masking of the evolution of primary and secondary lesions of syphilis in those whom this dosage fails to protect. It has not produced any increase in frequency of latent syphilis, as seen by serologic follow-up examinations, total cases, and a special

analysis of each latent case during 1950, but further investigations of this aspect are required. The report also shows that this usage of penicillin tends to encourage abandonment of mechanical and chemical prophylactic methods if indoctrination is careless. This, in turn, leads to increase of other venereal diseases—chancroid, nongonococcal urethritis, and, if extreme, syphilis as well. It is believed, however, that such carelessness can be largely overcome. Sensitization and sensitivity reactions to penicillin have not been much of a problem. In most cases reactions have been mild and have occurred after the patient took the first tablet. The severe penicillin reactions that have been reported have almost all been clearly due to intramuscular usage and have followed sensitization through intramuscular injections. Impressions that the oral use of penicillin causes sensitization have not been confirmed, according to this report.

GENERAL THERAPY

Since various antibiotics other than penicillin, as well as combinations of antibiotics, are being assayed for their value in syphilis therapy, certain papers of a more general character have appeared, which are reviewed here.

Antispirochetal Interference Between Antibiotics and Oxophenarsine Hydrochloride (Arsenoxide).—Ercoli and his co-workers recently reported that dimercaprol (BAL) inhibits the antispirochetal effect of penicillin, bacitracin, and chloramphenicol (Chloromycetin) as it does that of the metal-containing (As, Au) compounds, whereas streptomycin, chlortetracycline (Aureomycin), oxytetracyline (Terramycin), and subtilin are not inhibited by the dithiol. This dimercaprol reversal of antiprotozoan action is a specific one, inasmuch as the antibacterial action is conserved and seems to be related to the chemoreceptor mechanism. Exploring further the mechanism of antispirochetal action, Ercoli and Carminati [232] have studied the effect of combined treatment with known antiprotozoan agents. They found that the antispirochetal activity of arsenoxide was additively or synergistically enhanced by combined treatment with the antibiotics streptomycin, penicillin, or bacitracin. In contrast, simultaneous treatment with oxophenarsine hydrochloride and the antibiotics oxytetracycline, chlortetracycline, or chloramphenicol decreased both the immediate action of the antibiotic and the delayed action of the oxophenarsine. As a result of this interference with the early action of the antibiotics, the immediate antispirochetal effect of these combinations was lower than that resulting from antibiotic treatment alone. This phenomenon of interference with oxophenarsine activity appeared with effective, as well as with ineffective, doses of the antibiotics. On the other hand, the interference effect disappeared if the dose of either oxophenarsine or the antibiotic was increased sufficiently above the therapeutic range. Of the three antibiotics (chloramphenicol, chlortetracycline, and oxytetracycline) interfering with oxophenarsine, only chloramphenicol is inhibited (as are penicillin, bacitracin, and oxophenarsine itself) by dimercaprol in regard to its antispirochetal effectiveness. On the basis of the assumption that dimercaprol-reversibility is related to the action on chemoreceptors, Ercoli and Carminati conclude that the antibiotic interference with oxophenarsine is not bound to this action. In all their experiments, the interference phenomenon appeared as a decrease of activity of both drugs used for combined treatment (antibiotic and oxophenarsine). The phenomenon is mostly manifest at minimal-effec-

tive-dose ranges (or even below) and resembles a decrease of dosage in all its manifestations (reduction of the parasite count, relapses). To interpret their findings, Ercoli and Carminati arrived at the following working hypothesis, which seems to agree with the known facts and their present observations.

> *Therapeutic interference* is the result of a reciprocal competition between effective drugs in an *elective* process of fixation-penetration on or in the microorganism. This competition —which presumes a similar elective mechanism of fixation-penetration—reduces the concentration of the competing drugs below the levels required to affect the receptors to the point of measurable therapeutic response. The competition in the process of fixation-penetration can take place between drugs acting on identical or on different receptors, i. e. through the same or through a different type of biochemical lesion.

Each of the factors in this hypothesis is well documented in the original paper.

The Use of Antibiotics in Spirochetosis.—Laboratory and General Considerations: Magnuson,[233] in his usual thorough and critical manner, has reviewed the development of our present concept of the use of the antibiotics in the spirochetoses. As a by-product of the analysis of in vivo methods for evaluation of penicillin therapy, he points out that McLeod, working in his laboratory, has recently made the disturbing observation that the relatively low virulence of Treponema pertenue for the rabbit makes the results of node transfer in this disease much less reliable than in syphilis. The amount of penicillin required to cure experimental yaws is higher than that required to cure experimental syphilis. This recent observation on the questionable validity of negative node-transfer results adds further confusion to the picture. Keefer [234] in a somewhat general review of the antibiotics points out that

> It is plain that many problems have been solved in part and many new problems have become apparent. The search for new and better agents goes forward with the hope and expectation that the next decade of antibiotics may well prove to be the "Decade of Conquest."

Combined Antibiotic Action: The increasing number of available potent antimicrobial agents tempts the physician to use several of these drugs simultaneously in the same patient. This practice is often justified with the statement, "if one drug should not influence the disease-producing micro-organisms, the other one will." On the basis of the claim "if one drug is good, two should be better," combinations are frequently administered, although little is known about their effect. To approach this problem rationally, Jawetz and Gunnison [235] and their group assembled much data on the effects of drug combinations observed in the laboratory under controlled conditions. In no way does their report imply that the same principles will apply in clinical practice. The common and clinically useful antibiotics can be grouped as follows: Group I, penicillin, streptomycin, bacitracin, and neomycin; Group II, chlortetracycline, chloromycetin, and oxytetracycline. Members of Group I are frequently synergistic with each other, occasionally indifferent, never antagonistic. Members of Group II are neither synergistic with nor antagonistic to each other, but simple additive effects are often observed, presumably also obtainable by an increase in the dose of a single drug. Sulfonamides may fit into Group II. When a member of Group II is added to a drug of Group I, the combined result is a function of the relative susceptibility of the microbial strain to the drug in Group I and may be either synergism (in some cases when the organism is resistant to drugs in Group I) or even antagonism (in some cases when the organism is susceptible to drugs in Group II). For details of this complex matter, the original paper and its complete bibliography should be consulted.

Site for Intramuscular Injection: Augustine and his co-workers [236] favor the lateral aspect of the thigh as the site of choice for intramuscular injections. The area is easily accessible in all patients, is large, and contains no major vessels or nerves. Infection at the injection site is the most troublesome complication of this technique.

PHARMACOLOGY OF PENICILLIN

Duration of Penicillin Action in Relation to Its Concentration in the Serum.—Eagle and his co-workers [237] found no evidence in experiments with mice and rabbits that penicillin persists at effective concentrations in the uninflamed skin, muscle, testis, or peritoneal cavity for a significant period after it has fallen below those levels in the serum. When the duration of penicillin action was tested by inoculating normal animals (with streptococci and pneumococci) at varying intervals after a large intramuscular injection of penicillin, small challenge inocula proved infectious even before the serum concentration had fallen below 0.5 γ per milliliter. Their data support the idea that in the nonimmune animal the primary determinant of the therapeutic activity of penicillin is the total time for which it remains at the focus of infection in concentrations effective against the particular organism.

The Effect of the Interval Between Injections on Therapeutic Efficacy.—Eagle and his colleagues [238] found that small injections of penicillin sufficient to provide the maximally effective level at the focus of infection and repeated often enough to maintain the effective level continuously effected cure just as rapidly as massive doses similarly injected.

Transmission of Penicillin Through Human Placenta.—Raspe [239] gave 30 parturient women intramuscular injections of 400,000 units of penicillin immediately after they entered the delivery room, and, during delivery, blood was obtained from the arm vein of the mother and from the umbilical cord. The penicillin content of the serums was compared. The ratio between the serum content in the infant and in the mother increased up to three and one-half hours after the injection, at which time the penicillin content of the serum of the infant was equivalent to 60% of the penicillin content of the maternal serum. It is assumed that the penicillin passes through the placenta according to the laws of diffusion; the rapidity of transmission seems to depend on the size of the placenta. Soon after the injection of penicillin into the mother, the penicillin is excreted through the kidneys of the infant and appears in the amniotic fluid, its concentration in the amniotic fluid being higher than in the serum of the infant. The author emphasizes that it is not correct to speak of the penicillin content of the blood, because the penicillin content is ascertained in the serum and the penicillin content of the cellular portion of the blood is only a fraction of that of the serum. In the newborn serum accounts for 40% of the blood, and in adults, for 56%.

Treatment Failure with Penicillin.—Even large doses of penicillin continued for long periods of time may sometimes fail to effect cure in infections caused by organisms which, judged by their in vitro sensitivity, should have been readily controlled. Some of this failure may be due to the fact that the drug may not reach therapeutic concentrations in a walled-off or other focus into which the medicament cannot diffuse easily. In others the organism may have become resistant to the drug

during its prolonged administration. But in many cases there seems to be no adequate explanation. These statements not only apply to bacterial processes, but, according to Eagle,* the treatment failures observed in early syphilitic infection are even more surprising. It is true that T. pallidum is killed rather slowly by penicillin. It is however, one of the most sensitive organisms yet studied in terms of the minimal effective concentrations. As little as 0.002 to 0.005 mg. of pencillin per cubic centimeter has been estimated to exert a definite although slow treponemicidal effect both in vitro and in vivo. Nevertheless from 5 to 15% of the cases of primary or secondary syphilis are not cured by any schedule of treatment yet tried with various types of penicillin and with various time-dose relationships. Eagle therefore attempted to study in experimental infection (streptococcal) in mice some of the factors which may be responsible for these paradoxical treatment failures. He found that the organisms at the site of inoculation remained highly sensitive to the bactericidal action of penicillin only as long as they continued to multiply at a rapid rate. When the bacterial population in the muscle focus approached a plateau value, the bacteria simultaneously became refractory to the drug, and it required days to effect sterilization and cure instead of as many hours. The refractory state of the organism was not due simply to the number of organisms present in the older infection, and there was no evidence that a systemic host factor had been impaired. Further massive doses of aqueous penicillin which provided concentrations in the muscle 10,000 times greater than the minimal effective concentration were no more effective than the relatively low concentrations afforded by injection of penicillin procaine with aluminum monostearate. Eagle explains the refractory state on the basis that the organisms were no longer multiplying and metabolizing as actively as in the fresh infection.

Bismocillin, Theropeutic and Laboratory Experiments.—Helmeczi's group [242] used bismocillin (penicillin procaine, 1,200,000 units; bismuth salicylate, 0.20 gm.; aluminum monostearate 0.15 gm., and 0.01 helianthin solution to 5 cc.) in a short experience, with satisfactory immediate response (serologic) and with only rare reactions.

Penicillin in Combination with Bismuth and Arsphenamine (Salvarsan).—Bülow and his co-workers [243] stated that in vitro experiments show that penicillin is not inactivated by arsenical compounds or bismuth tartrate. Determinations of the penicillin concentration in plasma at different time intervals after injection of penicillin was carried out on a number of patients. Two days afterwards the same amount of penicillin was injected into the same patients, but bismuth subsalicylate, neoarsphenamine (Neosalvarsan), or both were injected at the same time; no significant difference between the two values was observed for the two days. This indicates that there is nothing to prevent the treatment of syphilis with bismuth, arsenic compounds, and penicillin injected simultaneously.

Clinical and Laboratory Observations on Penethanate Hydrochloride (the Hydriodide of Diethylaminoethyl Ester of Penicillin G; Neo-Penil).—In 1950, Jensen, Dragsted, and Kiaer,[244] in Denmark, prepared the diethylaminoethyl ester of penicillin G and noted that it reached high levels in lungs and sputum after parenteral

* References 240 and 241.

injection. Subsequently, they [245] showed that the hydriodide of this ester acted as a repository penicillin and also produced higher levels of penicillin in the lungs than either penicillin procaine or aqueous penicillin G (sodium salt). Grigsby, Haight, and Finland [246] showed that intramuscular injection of penethamate hydriodide (the hydriodide of diethylaminoethyl ester of penicillin G; Neo-Fenil) in aqueous suspension, a repository preparation of penicillin, results in significant concentrations of penicillin in sputum and other body fluids. The concentrations of penicillin in sputum and the ratio of these concentrations to those found in the plasma are higher after penethamate hydriodide than after similar amounts of aqueous suspensions of penicillin procaine or solutions of penicillin G potassium. Clinical and bacteriologic effects of penethamate hydriodide therapy in a small number of patients with acute pneumonia and chronic bronchopulmonary infections were favorable. Although these data are insufficient to indicate any superiority of penethamate hydriodide over penicillin procaine or the soluble salts of penicillin G, the higher concentrations of penicillin in sputum during penethamate hydriodide therapy and the fact that intramuscular injections of penthamate hydriodide appear to be better tolerated than other forms of penicillin suggest that it deserves further trial in bronchopulmonary infections due to penicillin-susceptible organisms. Undoubtedly reports of the use of penethamate hydriodide in syphilis will soon appear. Schimmel and his co-workers [247] found that penethamate hydriodide produces spinal fluid levels about 10 times greater than the levels produced by equal doses of other types of penicillin G in the same patients. They believe that this increased spinal fluid level is thought to be due to a pharmacologic property of the penethamate hydriodide rather than to an increased diffusion gradient. They also question whether or not the penicillin in the spinal fluid is active.

Paradoxical Effect of Penicillin.—Holtzman [248] studied a cutaneous lesion in an aged patient who had clinical evidence of syphilis of the central nervous system and also cardiovascular syphilis. Microscopic study of the lesion disclosed histologic features of syphilis and epidermoid carcinoma in situ. After penicillin therapy, there was a rather marked change in the relative degree of the inflammatory versus the neoplastic reactions. The inflammatory reaction seems to have been almost completely eradicated. The neoplastic element, on the other hand, seems to have lost all restraint, with cancerization of the entire epidermis and beginning invasion. Holtzman believes that this might be interpreted as another type of "paradoxical reaction" to specific therapy. The restraining effect here of an inflammatory reaction, specific in character because of the infected host but nevertheless restraining histologically, was removed by specific antisyphilitic therapy, allowing freedom of proliferation and invasion by the neoplastic process.

TREATMENT OF EARLY SYPHILIS

The therapy of early syphilis has been covered by a number of publications in this review period. Thomas [249] and Kampmeier [250] have presented discussions on the routine management of this disease. Although American practice finds it unnecessary to include other medicaments than penicillin, Teller [251] advises the combined use of 12,000,000 units of penicillin with one to two arsphenamine and bismuth courses for the therapy of early syphilis.

Oral Versus Injection Penicillin Therapy for Early Syphilis.—In 100 cases of primary or secondary syphilis treated at the Dermato-venereological Clinic of the University of Belgrade, Baryaktarovitch and Damjanovitch [252] employed four methods of therapy: penicillin alone, by injection or by mouth; penicillin and bismuth; penicillin and arsenic, penicillin, arsenic, and bismuth. The results of penicillin therapy were compared in respect of speed of disappearance of lesions, speed of serological reversal, and speed of disappearance of T. pallidum with those obtained with arsenicals and bismuth compounds. As regards serological reversal, it is concluded that the results of treatment with penicillin alone are not inferior to those of arsenic and bismuth and are superior when the antibiotic is associated with arsenic or bismuth, while from the bacteriological and clinical points of view penicillin, especially when combined with bismuth, gives better results than were obtainable by the older methods of treatment. The authors found penicillin to be as effective given by mouth as by injection.

Penicillin by Mouth and Fever in the Treatment of Early Syphilis.—Weinstein and his co-workers [253] have demonstrated the inadequacy of a treatment scheme for early syphilis consisting of 6,750,000 units of penicillin G sodium given orally and combined with a single six-hour session of physically induced fever. Success was achieved in 82% of patients with primary seronegative syphilis, 70% of patients with primary seropositive syphilis, and 52% of patients with secondary syphilis followed for 24 to 27 months after therapy. Cumulative failure rate at the 12- to 15-month observation period for secondary syphilis was 49.5%, as compared with 15.2% failures in patients with secondary syphilis receiving 4,800,000 units of penicillin in oil and beeswax given in divided doses of 600,000 units daily over a period of eight days.

Therapy of Early Syphilis with Artificial Fever in Combination with Oxophenarsine (Mapharsen), Bismuth, and Penicillin.—O'Brien and his colleagues [254] treated 163 patients with dark-field-positive lesions of early syphilis with a six-hour session of physically induced fever at 106 F., rectally; injections of crystalline penicillin G intramuscularly every two hours prior to the fever and hourly during the fever, to a total of 9,600,000 units; oxophenarsine, and bismuth. Total period of treatment was 30 hours. Follow-up of the patients revealed that this comprised good therapy. However, recent advances in repository penicillin therapy with one or only a few injections has already made this method obsolete, the authors state.

Seroresistance Following Treatment of Secondary Syphilis.—Thomas, DeMello, and Landy [255] point out that seroresistance following treatment of secondary syphilis occurs more frequently than is thought by many syphilogists. In view of their extensive material at Bellevue Hospital, 3.5% of their patients treated for seropositive primary syphilis and 27% of patients with secondary syphilis were still seropositive one year or more after treatment. In the absence of clear-cut evidence of relapse or reinfection, the duration of seropositivity after treatment of secondary syphilis cannot be shortened by increasing the duration or amount of penicillin treatment. In a series of 51 patients retreated one or more times because of prolonged seropositivity, only one was seronegative when last examined. The authors conclude that prolonged seropositivity after treatment of early syphilis in the absence of relapse, reinfection, or signs of progression of the disease does not mean a continuance of syphilitic infection.

TREATMENT OF EARLY SYPHILIS WITH OTHER THERAPY

Continued interest in the antibiotics other than penicillin is exemplified by the studies dealing with therapy as well as by the large volume of publications on reactions to this therapy, especially chloramphenicol (to be discussed later). There is practically no interest in the arsenicals or bismuth compounds used alone.

In a summary article based on the literature of his personal experience, Robinson [256] reviews the usefulness of the new antibiotics in the treatment of venereal disease. The preparations considered are cortisone and corticotropin (adrenocortitrophic hormone; ACTH), chlortetracycline, chloramphenicol, and oxytetracycline. Syphilis, gonorrhea, granuloma inguinale, chancroid, lymphogranuloma venereum, and yaws comprise the venereal diseases discussed.

As a result of a two- to four-year follow-up of patients treated for primary or secondary syphilis with chloramphenicol, chlortetracycline, or oxytetracycline, Robinson and Robinson [257] conclude that these broad-spectrum antibiotics are of value as antisyphilitic agents in patients who are sensitive to penicillin and who can be kept under supervision. Analysis of their findings, however, leads us to the conclusion that their results are definitely inferior to those obtained with penicillin. Of 30 patients treated with these various antibiotics, followed for two to four years, only 18, or 60%, were seronegative at the time of the last examination. Seven, or 23%, were seropositive or serodoubtful, and 5, or 17%, had sustained relapse. On the basis of these findings, the broad-spectrum antibiotics should be considered definitely inferior to penicillin for antisyphilitic therapy.

Treatment of Early Syphilis with Chlortetracycline.—Rodriquez and his coworkers [258] report the results of their observation for 12 to 15 months on 101 patients with dark-field-positive secondary syphilis. Chlortetracycline in the following treatment schedule was administered by the oral route to each of the 101 patients: An initial priming dose of 2 gm. was given, and this dose was repeated four hours later; then 1 gm. was given every four hours, day and night, until a total of 70 gm. had been administered in 11⅓ days. The cumulative percentage of treatment results at the end of the 12- to 15-month observation period were as follows: 76.7% cases were classified as successes (comprising 66.2% seronegative and 10.5% with 3 Kahn units or less in the serum); 2.1% were classified as reinfections, and 21.2% were classified as failures (comprising 7.0% clinically normal but with 4 Kahn units or more in the serum and 14.2% declared clinical or serologic failures).

Seven patients became pregnant after treatment and were not retreated. Of these pregnancies, five terminated in live births (all were clinically, serologically, and roentgenologically normal) and two in fetal deaths (one a criminal abortion, the other a spontaneous abortion of nonsyphilitic origin).

Treatment of Early Syphilis with Oxytetracycline.—Irgang and Alexander [259] report on the treatment of 10 patients with early acquired syphilis with orally administered oxytetracycline, 2 gm. per day for 14 days. They conclude that oxytetracycline is of value in the treatment of syphilis in the dosage used and that it may be substituted for intramuscular injections of penicillin when the latter is contraindicated, but they add the curious statement that it should be used conjointly with bismuth. It is our feeling that their findings do not warrant their conclusions. Only five patients were followed for three or more months after treat-

ment, and only three patients were observed to have become seronegative. Conclusions based on such short follow-up of few patients should not be accepted as valid.

Intramuscular Chloramphenicol in the Treatment of Venereal Disease.—Olansky and his co-workers [260] have studied the effect of intramuscular administration of chloramphenicol in the treatment of the five venereal diseases. Sixty-three patients with primary or secondary syphilis, treated with 2 gm. every 12 hours for six days, a total of 24 gm., or 2 gm. daily for six days, a total of 12 gm., followed for three months or more, showed favorable serologic results. Of the 40 patients observed 6 to 13 months, 35 were seronegative at the time of last examination and in 5 the titer was declining. Treponemal immobilization tests were positive in 7 of 18 patients with primary syphilis and in 23 of 28 patients with secondary syphilis. In 23 patients with granuloma inguinale treated with 12 gm. of chloramphenicol lesions were completely, or nearly completely, healed on discharge. On follow-up examination, only one failure has been observed. Six patients with chancroid had complete healing after therapy. Lesions of lymphogranuloma venereum improved after treatment in two patients. A single patient with gonorrhea was also cured. Although no cases of blood dyscrasia were seen, the authors emphasized the importance of keeping this grave complication of treatment in mind. The authors conclude that intramuscular chloramphenicol seems to be an effective therapeutic agent in the treatment of all five venereal diseases.

Experiences with the Arsenobenzol Preparation Spirotrypan (Höchst) in Syphilis.—Ledig [261] has used the arsenobenzol preparation Spirotrypan (Höchst) since 1939 on 123 patients (43 men, 68 women, and 12 children). It is as active therapeutically as the usual arsenicals. It is extremely well tolerated and convenient to use.

TREATMENT OF LATENT AND LATE SYPHILIS

According to McElligott [262] the death rate from syphilis during the next 30 years will depend largely on the discovery, management, and treatment of the thousands who must be at large in the, as yet, asymptomatic phase of late infection. It is during this stage that so much can be done to heal permanently the still hidden chronic inflammatory processes and, even when disease is apparent, to halt the advance of these processes, even though resulting fibrotic and degenerative changes in the affected tissues are naturally irreversible. Latent syphilis, however, is never an emergency, and once nervous and cardiovascular involvement has been excluded the danger of delaying treatment for weeks or months is negligible. Tests giving unexpected positive blood findings must always be repeated, and the possibility of false-positive reactions and of technical or clerical error in the laboratory or elsewhere kept in mind. Except in pregnancy, it is nearly always wrong to commence treatment in doubtful cases in order to "play for safety." Once a diagnosis has been reached, the patient must be told the truth; vague allusions to a "blood condition," or some such euphemism, must not be made to spare his feelings. The significance of seroresistance and, indeed, of its probability in spite of the best treatment, should be explained at an early stage, to prevent the patient's wrongly interpreting persistently positive blood reactions as a lack of response to treatment. Late syphilis, especially when the "vital systems" are not apparently involved, must not spoil lives; there is, in fact, no condition in which the physician can afford to be so

optimistic. The results to date of penicillin treatment are excellent, though one must, of course, distinguish between the chronic inflammatory process, which is usually healed, and the resulting fibrosis and structural changes, which in certain situations may shorten life in spite of the best treatment. The author abandoned use of arsenicals in the treatment of all stages of syphilis in 1947 and so far has had no cause to regret his decision. He believes that penicillin is the safest and most powerful treponemicidal agent yet known, that the progress of late syphilis can in most cases be rapidly halted by its use, and that its true value will only be known when careful clinical, cardiographic, and pathological follow-up is substituted for the blind continuous, so-called "insurance," treatment, so popular in the past, and when postmortem study of treated cases becomes the rule rather than the exception.

Studies of Syphilis of the Ear and Penicillin.—In a detailed presentation Ittkin and Tamari [263] again reviewed the subject of syphilis of the ear and the influence of penicillin on this phase of syphilology. They also present a clinicostatistical analysis of the results obtained in the study of the otologic manifestations of 310 patients with an established diagnosis of syphilis. They found that early and adequate penicillin therapy in early and latent syphilis prevents eighth nerve deafness. Probably one of the outstanding and most satisfying results of penicillin is the almost 100% effectiveness in its prevention of prenatal syphilis. All evidence indicates that syphilis of the inner ear and eighth nerve will in the near future decline to an insignificant level with the help of penicillin.

Syphilitic Osteomyelitis Treated with Penicillin.—In their paper reporting their total experience with antibiotic and chemotherapeutic agents in infections of the skeletal system, Altemeier and Largen [264] mentioned three cases of osseous syphilis. A review of their 3 cases and 22 other cases previously reported indicates that penicillin is beneficial in early syphilitic lesions, affording prompt systemic relief within 2 to 10 days and resulting in evidence of progressively accelerated healing. From the available reports, the sites of predilection of destructive syphilitic lesions appear to be the skull, the bones about the sternoclavicular joint, and the long bones, in that order. The clinical response in their cases was moderately slow but good, and apparently complete healing occurred.

TREATMENT OF CARDIOVASCULAR SYPHILIS

At last it would seem that the treatment of cardiovascular syphilis has been consolidated on a firm basis. There are a number of general discussions.† Ambulatory therapy is now considered safe, and a number of treatments for various types of aneurysms have been explored.

Beerman ‡ has reviewed the present-day therapy of cardiovascular syphilis. He believes that in the present state of knowledge any evaluation of a new mode of therapy for cardiovascular syphilis is bound to yield inconclusive results. This frustrating situation is due to the many unsolved problems in the diagnosis of cardiovascular syphilis and to the fact that the interpretation of the actual effects of the therapeutic measures under investigation cannot be appreciated fully because of the lack of suitable controls. This review was undertaken, therefore, with due

† References 265-271.

‡ References 267 and 268.

cognizance of the tentative and relative character of the data presented but, however, with the full conviction of the reviewer that in penicillin practitioners have at last a safe effective means of supplementing the equally important medical aspects of treatment of cardiovascular syphilis. From the compilation of the literature on penicillin therapy of cardiovascular syphilis it is apparent how groundless are the fears originally expressed that this mode of treatment would be productive of an excessive number of therapeutic shocks and paradoxes. Encouraged by the relatively lessened tendency to cause reactions of penicillin G over that of the cruder product, the University of Pennsylvania group, in May, 1949, reported the results of the treatment of 50 cases of cardiovascular syphilis with penicillin therapy alone, without preparation; there were 12 patients with cardiovascular syphilis and congestive failure, in whom penicillin and methods to combat congestive failure were used simultaneously. In this group not only were untoward effects lacking but the distinct impression prevailed that these patients responded better than most patients with cardiovascular syphilis and decompensation who were treated, as was often the case in the prepenicillin era, with measures aimed only toward combating congestive failure. Experience with these two groups of cases led to the belief that therapeutic shock in cardiovascular syphilis treated with penicillin is indeed uncommon and that therapeutic paradox, if it occurs, is a rarity.

Subsequently this group has reported observations on 111 patients with penicillin-treated cardiovascular syphilis (simple aortitis, 48 cases; aortic regurgitation, 51 cases; aortic regurgitation and aneurysm, 9 cases, and aneurysm, 3 cases) with reemphasis of the virtual absence of significant therapeutic shock and paradox.

The serologic effects of penicillin therapy on cardiovascular syphilis are bound to be disappointing. The frequent association of neurosyphilis with syphilitic cardiovascular involvement (for example, 45.2% of the 111 University of Pennsylvania patients also had central nervous system syphilis) may account for much of the poor serologic effect of treatment. The University of Pennsylvania group (March, 1951) found, disregarding the 6 cases without follow-up, that there were 85 cases positive before treatment and 86 cases positive after therapy. Twenty cases were negative before treatment, and 19 cases were negative after treatment. Although 7 of the cases with a positive serologic reaction had negative reactions after treatment, 8 of the original 20 cases that had negative reactions prior to treatment had positive serologic status after penicillin therapy. Thirty-six of the 85 patients with positive test results showed a drop of two or more tubes in the quantitative test. Thirty-seven of the 85 showed no change in the quantitative tests.

The University of Pennsylvania group found that

> Penicillin is admirably tolerated by the decompensated heart, with clinical improvement in a high proportion of cases. Anginal pain was relieved without recognizable shock or paradox in 4 out of 5 cases. In syphilitic aortitis "uncomplicated," observed for from 3 to 58 months one-third are improved, one-half unchanged and only one-sixth were worse (one death of bronchopneumonia). In aortitis with regurgitation 64 percent are improved, 20 percent unchanged and 16 percent are worse. In aneurysm with regurgitation the number is too small for analysis, but 4 or 5 kept under observation improved. Of 3 large saccular aneurysms, one lapsed from observation, one died in a wiring operation, and one was unchanged.

With respect to the electrocardiographic changes produced by penicillin in the treatment of cardiovascular syphilis, there are only scattered data, the exact significance of which is not clear.

Are there any contraindications to the use of penicillin in cardiovascular syphilis? Patients exhibiting a variety of processes, previously contraindicating arsenical therapy, have been given penicillin treatment without serious untoward effects.

Should patients with suggestive, but not positive, signs of aortitis be treated with penicillin? The answer is yes. In view of the uncertainties of diagnosis of uncomplicated syphilitic aortitis and the safe and probable effectiveness of penicillin therapy, the patient should be given the benefit of the doubt, not only because it is practically without danger but also because it is inexpensive and not time-consuming. In the past many patients were not treated because even presumptive diagnosis condemned them to a prolonged, costly, and even dangerous therapeutic regimen. Is treatment with bismuth and iodides necessary prior to penicillin therapy of cardiovascular syphilis? Although most British physicians are employing such preparatory treatment, this seems unnecessary from the reaction standpoint, at least. Whether the eventual outcome of treatment will be better with combined therapy or penicillin alone is still unanswered.

Assuming that penicillin therapy is the safest agent yet produced for cardiovascular syphilis, we suggest that the treatment scheme of the University of Pennsylvania group be employed until a more convenient or effective regimen is evolved.

The advocated treatment includes hospitalization, two-hour schedule, crystalline penicillin G (4,800,000 to 9,600,000 units in 40,000 to 80,000 unit individual doses), but procaine penicillin may be given to hospitalized patients on a 600,000 unit single, or 300,000 unit two-injection daily schedule for equal total dosage. The ambulatory use of this salt is under investigation. By present standards, repetition of courses in excess of two of 9,000,000 units seems unnecessary. The concomitant or subsequent use of heavy metal was not studied in this series, but seems on general experimental grounds to be unnecessary.

Further Observations on Penicillin-Treated Cardiovascular Syphilis.—The purposes of a study by Edeiken, Ford, Falk, and Stokes[269] were (1) to determine to what extent penicillin is tolerated by patients with cardiovascular syphilis, including those with congestive failure or angina pectoris; (2) by prolonged follow-up studies, to determine the frequency of therapeutic paradox and the influence of penicillin therapy on the subsequent course of the disease. A total of 111 patients were treated, first with very small doses and later with 40,000 to 80,000 units of aqueous penicillin every two or three hours until 4,800,000 to 9,600,000 units were given. No evidence of either therapeutic shock or paradox was found, although some of the patients developed a mild fever. The authors concluded that it does not appear to be dangerous to treat patients with cardiovascular syphilis with penicillin.

Penicillin in Cardiovascular Syphilis.—One of 11 patients with cardiovascular syphilis treated with penicillin by Ellegast and co-workers[270] (total dose 6,000,000 units) died in the course of the treatment, and 3 had symptoms of circulatory decompensation during treatment or immediately thereafter and died within eight weeks. Necropsy revealed aortic insufficiency in three of the four fatal cases. The Herxheimer reaction did not seem to be a cause of death, nor was occlusion of coronary vessels revealed at necropsy. In two of the fatal cases a myocardial lesion was considered as the only cause of death, and it may have contributed considerably to death in two other cases. Despite the satisfactory results with penicillin in patients with cardiovascular syphilis reported on by American workers, the authors believe

that treatment of cardiovascular syphilis with penicillin as well as with arsphenamine is not without risk, partly because of the acute changes in tertiary syphilitic granulations in the cardiovascular system, with resulting thromboses and circulatory disturbances, and partly because of the possibility of a flare-up of syphilitic manifestations. Treatment with penicillin should, therefore, be limited to certain cases, and precautionary measures are required. Preparatory treatment with smaller doses of iodine and a sterile oily 5 or 10% emulsion of bismuth subsalicylate should precede treatment with penicillin. Patients with decompensation or coronary symptoms should be excluded from treatment with penicillin.

The Specific Treatment of Syphilitic Aortitis.—Kampmeier and Morgan [271] agree that penicillin has made the specific treatment of cardiovascular syphilis easy to give and easy to take and has all but abolished dangerous treatment reactions. Just as the curative therapy of acute syphilis with penicillin is simple and feasible, so is the prophylactic treatment of cardiovascular syphilis in persons with latent syphilis and uncomplicated syphilitic aortitis simple and feasible. In spite of the fact that the effectiveness of such treatment has not been conclusively established, the prospects seem bright that the incidence of cardiovascular syphilis will decrease sharply in the immediate future. Cardiovascular syphilis may be treated, with or without preliminary bismuth and iodide "preparation," by the administration of 4,800,000 to 6,000,000 units of penicillin in a period of 8 to 10 days. Larger doses and longer periods of treatment have been employed. Experience thus far does not indicate that penicillin therapy of established complications of syphilitic aortitis will be any more successful than was therapy of the prepenicillin era.

Ambulatory Treatment of Cardiovascular Syphilis with Penicillin.—Edeiken and his co-workers [272] report upon ambulatory treatment with penicillin procaine in 19 patients with cardiovascular syphilis. Patients received 6,000,000 to 9,000,000 units in 9 to 19 days. There was no evidence of therapeutic paradox and, except for a slight rise in temperature in one patient, no evidence of therapeutic shock. The authors conclude that administration of penicillin on an ambulatory basis to patients with cardiovascular syphilis is a safe, practical, convenient, and inexpensive method of therapy.

Surgical Treatment of Aneurysm.—DeBakey and Cooley [273] report the successful resection of a huge, probably syphilitic, aneurysm of the descending aorta in a 46-year-old white man. The aneurysm produced extensive erosion of the vertebral bodies and incapacitating symptoms. Normal blood flow was restored by means of an aortic homograft following removal of the aneurysm along with the involved segment of the aorta. Although the aorta was occluded for a period of 45 minutes during the anastomosis, there were no residual manifestations of ischemic changes in the spinal cord, the kidneys, or other organs.

An extensive review of the literature is made, with particular reference to etiology, symptomatology, diagnosis, treatment, and prognosis. Saccular aortic aneurysms are usually caused by syphilis. They occur in middle-aged patients and arise above the origin of the renal arteries. Trauma or infection other than syphilis is responsible for an occasional aneurysm which, except for the absence of diffuse aortitis, clinically resembles those due to syphilis. Arteriosclerotic aneurysm of the aorta almost invariably occurs in the terminal aorta, below the origin of the renal arteries. The authors consider the historical aspects and advantages and disadvan-

tages of the methods of surgical treatment which have been used. These include ligation, wiring, use of fibrogenic or reinforcing materials about the aneurysm, endoaneurysmorraphy, and excision. Case reports are presented for eight patients with saccular aneurysms in different regions of the aorta. Of these, six had either positive serologic tests for syphilis or a history of the disease. Excision of the sac and suture of the aorta have been successfully carried out in six of the eight patients in this study. The surgical technique is also discussed.

Results of Polythene Wrapping of Aortic Aneurysms.—After a review of the literature, Hume [275] reports on 12 patients who had aneurysms of the thoracic or abdominal aorta or of the innominate artery. The 12 patients ranged in age from 39 to 69 years. Of the group, 9 were men and 3 were women. Seven patients had syphilis, confirmed by serologic test, while an additional patient had had treatment many years before. Brief case reports are presented for the 12 patients. In each patient the aneurysm was wrapped with polythene. The results obtained to date are discussed, and the opinion is expressed that the procedure is of value. Results can be improved by earlier detection and operation.

An Analysis and Follow-Up Study of One-Hundred Popliteal Aneurysms.—Surgical treatment designed to obliterate, reconstruct, or extirpate a popliteal aneurysm carries by far the best prognosis. The procedure of choice, in the opinion of Gifford, Hines, and Janes,[276] is lumbar sympathectomy followed immediately by extirpation of the aneurysm. Only one period of anesthesia should be used.

Excision of Syphilitic-Arteriosclerotic Aneurysm.—Hardy [277] described the history of a 54-year-old Negro who was diagnosed as having an innominate aneurysm. Past history revealed a penile chancre 18 years previously. Laboratory tests showed a positive blood serology. A successful excision of the syphilitic-arteriosclerotic aneurysm of the innominate artery was made; however, the patient died of acute heart failure during the second 24-hour period following the operation.

TREATMENT OF NEUROSYPHILIS

The material on the therapy of neurosyphilis is especially barren of new ideas, yet certain review articles, one by the late Dattner and his colleague, Green,[278] one by Miescher and Brenn, of Zurich,[279] one by Nicol,[280] and one by Kierland [281] all agree that penicillin therapy is the best treatment for neurosyphilis. Kierland's statement is worthy of more extended mention. He gives a total dose of at least 6,000,000 units of penicillin over a period of at least 10 days as a first course. The schedule may be varied. As examples, 600,000 units may be administered daily for 10 days; 300,000 units daily for 20 days, or 600,000 units of repository penicillin daily, every other day, twice a week, or even less frequently. One course is generally adequate. A poor response may indicate the need of a second similar or more intensive course. Only rarely is a third necessary. If two courses of penicillin fail to effect good results, fever therapy, especially malarial, or another antibiotic, such as chlortetracycline, should be considered. Chlortetracycline should probably be reserved for patients who are hypersensitive to penicillin or whose disease is resistant to penicillin. Chlortetracycline in a total dosage of approximately 60 gm., administered as 2 to 4 gm. per day in divided doses, yields results equivalent to those achieved by a first course of penicillin. When chlortetracycline causes gastrointestinal symptoms, continuation of medication may be possible with reduced daily

dosage. Oxytetracycline and chloramphenicol are also valuable against neurosyphilis, but the latter may cause hemopoietic suppression. If the patient has optic atrophy or severe paresis, the first course of 6,000,000 units of penicillin should be accompanied by fever therapy. In the diagnosis of neurosyphilis, clues are furnished by a complete and accurate history; a comprehensive physical examination, including thorough neurologic studies; serologic tests, and examination of the cerebrospinal fluid. Nothing substitutes for a high index of suspicion of the disease before neurologic changes are irreversible as in obvious cases of paresis or locomotor ataxia. The diagnosis of active neurosyphilis rests primarily upon the finding of abnormalities in the cerebrospinal fluid. In order of importance, these are (1) increased cell count, (2) increased concentration of protein, (3) positive serologic reaction for syphilis, and (4) abnormal reaction in the colloidal gold test. Diagnosis of activity is more difficult in cases of vascular neurosyphilis, syphilitic epilepsy, gumma of the brain or spinal cord, eighth nerve deafness, or optic atrophy without paresis, since the spinal fluid may be normal in all these conditions. In many of these cases, diagnosis may be made by clinical trial of penicillin with or without fever therapy. The spinal fluid should be examined four to six months after the completion of treatment. If the increased cell count has reverted to normal or near normal, the amount of protein has decreased, and the patient seems improved, no further treatment is needed. The complement-fixation reaction and results of the colloidal test may not revert to normal for several months or years and cannot be used to gauge adequate treatment. Lack of clinical evidence of improvement does not mean that treatment has been ineffective, since many changes may be irreversible and persist without active disease. On the other hand, the patient's symptoms may be ameliorated in spite of continuing active disease. If, however, the cell count and protein value remain high, a second course of therapy is mandatory. The second course should be the same as, or more intensive than, the first one. When the response is favorable, the spinal fluid should be examined at intervals of four to six months for the first year after treatment, then yearly until the spinal fluid is no longer abnormal.

Corticotropin Therapy of Lightning Pains and Visceral Crises.—Moore [282] points out that tabes dorsalis differs from all other forms of neurosyphilis in the extraordinary selectivity of the pathologic process, the tendency of the disease to occur only in persons of asthenic habitus, the longer incubation period, the lesser immunologic response in terms of blood and spinal fluid reagin titer, the paucity or absence of T. pallidum in the lesions, and the refractoriness to treatment. In five tabetic patients with intractable lightning pains, administration of corticotropin or cortisone lessened the frequency and severity of attacks of pain. In two patients with gastric crises, the results of treatment with cortisone were equivocal. Moore emphasizes that these hormones should not be used in the treatment of the average patient with tabes dorsalis. Fully aware of the possibility of spontaneous arrest of the symptoms in patients with tabetic crises, Weiner and Mendelsohn [283] also report a case in which it appears most probable that intravenously administered corticotropin was responsible for a rather dramatic response. Relief was observed on the eighth day in a matter of hours after the initial dose of corticotropin. Since intravenous administration of dextrose alone has been known to be followed by relief of crises, it is noteworthy that this did not occur until the corticotropin was added in this instance.

Management of Vesical Dysfunction of Neurosyphilis by Transurethral Resection of the Vesical Neck.—On the basis of his own experience with three cases so treated, Fowler [284] advocates transurethral resection for therapy of syphilitic cord bladder.

TREATMENT OF OCULAR SYPHILIS

Syphilitic Optic Nerve Atrophy Treated with Penicillin.—Benton and Harris [285] have produced evidence to show that penicillin is of value in the treatment of early syphilitic optic atrophy. A series of 23 patients was treated with large doses (4,000,000 to 8,000,000 units) of penicillin and followed for four years. If vision was 20/50 or better at the start of treatment, further visual loss was prevented. If vision was worse than 20/50 at the start, progressive visual loss occurred despite treatment. In the latter group of cases, larger doses of pencillin or penicillin plus fever therapy might be tried.

TREATMENT OF SYPHILIS IN PREGNANCY AND CONGENITAL SYPHILIS

The following investigations indicate the great impact penicillin therapy has had in reducing the incidence of congenital syphilis. In spite of the still enthusiastic reports, there appear to be some investigators who feel somewhat disappointed with their results.

In a provocative study, Nelson and Struve [286] challenge a statement recently made that the number of cases of congenital syphilis reported has remained approximately constant for the past five and one-half years. They demonstrate a marked decline in both morbidity and mortality reports from congenital syphilis in white and Negro persons in the city of Baltimore since 1921. There has been an equally striking decline in the national mortality from congenital syphilis. On the basis of these findings, the authors state:

> Since the decline in the infant mortality rate is the sum of the effect of better and wider use of therapy and a decline in morbidity, and since the effect of therapy in Baltimore may be assumed to be as least equal to that in the United States as a whole, it may be deduced that the infant morbidity rate in the United States has declined at least as rapidly as it has in Baltimore during the past 15 years or more.

The authors explain the failure of the national congenital syphilis morbidity rate to drop by better case finding of older persons with congenital syphilis. An analysis of 31 recent cases of congenital syphilis indicates that in 17 cases the mother had no prenatal care until the last week of pregnancy, in 4 there was reinfection or relapse near the time of delivery, in 6 the mother's infection was known in time but not treated, and in 2 the condition was probably erroneously diagnosed. Nelson and Struve conclude that the time has almost come when there can be no further reduction in the infant morbidity rate from syphilis except as the incidence of syphilis in pregnant women declines or as more women seek prenatal care in time to have their infections discovered and treated during pregnancy. They point out that a premarital blood test law would not have prevented a single one of these congenital infections.

Among 1,002 syphilitic women treated with penicillin, Shaffer and Courville [287] found the incidence of abortion, miscarriage, stillbirth, and neonatal death similar to that reported for nonsyphilitic pregnancies. Four stillbirths and one neonatal death were attributed to syphilis, and there were five congenitally syphilitic infants born. Relapse or reinfection late in pregnancy were responsible for one-half of these

syphilitic accidents. Shaffer and Courville conclude that syphilitic women who have been adequately treated and who have either progressed to seronegativity or to a low titer need not be retreated in subsequent pregnancies. However, they advise retreatment of the seropositive pregnant women when "there is any question of unsatisfactory response to previous therapy or of the patient's willingness to remain under close observation." It is emphasized again that a positive cord STS is not diagnostic of congenital syphilis. Only four of the 137 positive cord bloods of the infants were found to be syphilitic. Of 91 infants vaccinated against small-pox within the first five days of birth, there were only three who were seropositive at the age of three to four weeks, and the authors believe that this seropositivity probably represented passive transfer of reagin from the mother's blood rather than biologic false positivity due to vaccinia. In summary, the authors conclude that adequate penicillin treatment during pregnancy is nearly 100% effective in the prevention of congenital syphilis or in curing an already infected fetus, provided further serologic and clinical progress of the mother and infant is satisfactory.

In a study from the pediatric clinic of the University of Naples, Auricchio and Vecchio [288] point out that the total fetal loss in noncured syphilitic mothers (formerly between 24 and 35%) is now, thanks to penicillin treatment, only 10 to 12% and also that penicillin has reduced the incidence of congenital syphilis from 56 to 1 or 2%. Optimism, they feel, is therefore justified. At the same time, however, they doubt whether seronegativity in the offspring justifies the classification of these children as nonsyphilitic, especially those born from mothers in the quiescent stage of the disease or with an apparently cured old infection which was never treated. In this study the authors subdivided their series of 170 newborn and young infants into three groups: (1) healthy; (2) infected, and (3) serologically negative but clinically suspect. It was found that, whatever phase of the disease the mother was in during pregnancy and irrespective of whether treatment was instituted early or late in pregnancy, the largest group of infants was always those who were seronegative but clinically suspect. In a discussion of this finding the authors ask to what extent seropositivity in the newborn is due to transplacental passage of antibody. It is their view that flocculating antibodies are complete antibodies and cannot pass the placental barrier but that complement-fixing antibodies can do so. Therefore the former always indicate active infection. Seronegativity offers greater difficulty in the interpretation; cases are mentioned in which seropositivity and/or enlarged spleen, hydrocele, hydrocephalus, and retarded development appeared later. The authors, supported by references to the literature, postulate that there is a distinct order of appearance and of disappearance of antibodies, namely: (1) immobilizing antibody of Nelson and Mayer; (2) T. L. reagin (thermolabile protein reagin); (3) T. S. reagin (thermostable, polysaccharide; (4) antilipoid reagins giving the common reactions and appearing last, that is, up to six to eight months after tests for thermolabile and thermostable antitreponema antibody have become positive. In treatment with penicillin these antilipoid antibodies become unavailable, possibly because of a state of equilibrium between the spirochete and the body, long before the antitreponemal antibodies disappear; in this way a false conclusion as to seronegativity is drawn. The authors thus believe that penicillin treatment of the expectant mother leads to a clinical serological quiescence rather than to real biological cure. However, they prefer to reserve final judgment until a much larger series of cases has been examined.

On the other hand, Enkvist [289] investigated the problem of whether specific treatment of a syphilitic mother during pregnancy affects the prognosis of her offspring. Data were obtained on 555 children with congenital syphilis who could be classified in two groups according to whether the mothers had received specific treatment with bismuth and arsphenamine during their pregnancies. There were 102 children in the first group and 453 in the second. Specific treatment during pregnancy may better the prognosis for the syphilitic offspring, but the benefits obtained are not as great as expected.

Serological Findings in Pregnancy Syphilis Following Penicillin Therapy.—Anzisi [290] studied the reactivating effects of penicillin (penicillin in wax with procaine and aluminum monostearate) on serological findings for syphilis in 272 pregnant women. The activation was observed in 15.8% of cases.

TOXIC REACTIONS TO PENICILLIN TREATMENT

Although there still is some resistance to the idea that penicillin reactions are on the increase, the opponents of this idea are now faced with a rising number of reports dealing with fatalities to this drug. However, one must realize that, while such reactions, severe and fatal, are on the increase, they are few in proportion to the number of patients treated, and the aggregate of benefits from penicillin is so great that one should not condemn the preparation. These reactions are merely lending further support to the warnings from here and elsewhere against indiscriminate use of the antibiotics, especially penicillin. It is of interest that fatalities from penicillin therapy of syphilis are practically nonexistent. This may be due to the relative youthfulness of the patients and their generally, except for the syphilis, good health. Another factor in the rise of severe or fatal reactions is the introduction of a new penicillin derivative, penethamate hydriodide (Neo-Penil).§

A survey of the current literature on penicillin reactions reveals good surveys of penicillin sensitivity by Lindemayr [294] and by Finland and Weinstein [295]; a case of acute preliminary edema,[296] and anaphylaxis, fatal and nonfatal.|| An interesting effect of penicillin is the occurrence in patients with severe penicillin reactions of the L. E. factor in the plasma and L. E. cells in the bone marrow.[306] Triantaphyllopoulos and Waisbren [307] could find no effect from penicillin on blood coagulation. Davis [308] obtained symptomatic relief and clinical improvement with cortisone for patients with cutaneous penicillin reactions resistant to routine therapy.

JARISCH-HERXHEIMER REACTION TO PENICILLIN

This review period has seen chiefly consolidation of previous observations on the Jarisch-Herxheimer reaction to penicillin.[309] Stimulated by previous studies which indicated that there were definitive microscopic changes in syphilitic lesions in men and in rabbits in association with a clinical Herxheimer reaction, Putkonen and Helle [310] investigated the occurrence of a febrile Herxheimer reaction and of a macroscopic local Herxheimer reaction in experimental rabbit syphilis. Twenty-seven rabbits were inoculated intracutaneously in the back at two points side by side with 3×10^5 spirochetes and intratesticularly (right testis) with 7.5×10^5 spirochetes; syphilis developed in all rabbits. The average incubation period was

§ References 291-293.

|| References 297-305.

12.7 days for the cutaneous lesions and 12.6 days for orchitis. The serologic incubation period was 14.5 days for the Kahn test and 24.0 days for the Wassermann test. Each syphilitic rabbit was given a subcutaneous injection of 2,000 units crystalline penicillin per kilogram of body weight in pyrogen-free water 5, 10, 20, 30, 40, 60, or 90 days after inoculation. After penicillin treatment the rectal temperature of the rabbits was recorded at hourly intervals for 24 hours, using a technique employed in pyrogen determinations. The syphilitic lesions were examined 6, 12, and 24 hours after each injection for changes indicative of a local Herxheimer reaction. The absence of febrile and macroscopic Herxheimer reactions in rabbits is one of the features distinguishing rabbit syphilis from the human disease.

In a case of cardiovascular syphilis reported by Retbøll [311] a severe febrile reaction and acute cerebral symptoms developed after the institution of penicillin therapy. The patient died six days later. Autopsy showed that the cerebral tissue was the site of numerous hemorrhages, and Retbøll considered this to be a fatal Herxheimer reaction from penicillin. Kuster and Bechmann [312] have made efforts to determine the dosage of penicillin which will control the occurrence of the Herxheimer reaction in congenital syphilis.

TOXIC REACTIONS NOT DUE TO PENICILLIN

In spite of the advantages of penicillin therapy there are still instances of fatal reactions in the recent literature resulting from the use of bismuth [313] and arsphenamine.[314] Odin [315] has reported a study of the incidence and nature of hepatitis, made at the Sahlgrens Hospital in Gothenburg during the past 15 years. The author believes that it has not been possible to draw any definite conclusions from the study as to the frequency of syringe infections, except in the case of blood transfusions and of syphilitic patients treated with bismuth and arsenic. During the past four years 48 cases of hepatitis associated with antisyphilitic injections were observed.

TOXIC EFFECTS OF ANTIBIOTICS OTHER THAN PENICILLIN

It is well established that chloramphenicol can produce serious fatal hemopoietic reactions,¶ as well as other reactions.# It is necessary for the physician to realize that these blood reactions are not to be expected with certain of the antibiotic preparations. In this case one must understand that a small but definite calculated risk must be taken when chloramphenicol as well as other antimicrobial agents are administered.

The question of the relationship of fungus infections to the use of these compounds is also not settled. Some [327] have reported fatal fungus infections as complications of antibiotic therapy. In the same vein, David T. Smith,[328] of Duke University, states that

> Evidence is accumulating to show that the complex balance which exists among microorganisms constituting the normal flora of the body is disturbed by the prolonged administration of the newer antibiotics. This may result in the development of secondary vitamin deficiencies or the evolution of new infectious disease syndromes.

Although this phenomenon has not been too great a problem in syphilotherapy, Smith's observations are worthy of note. He found that prolonged therapy with

¶ References 316-324.

References 325 and 326.

penicillin suppresses or eliminates Gram-positive bacteria and stimulates directly or indirectly the multiplication of Gram-negative bacilli. Prolonged therapy with relatively large doses of streptomycin may suppress the Gram-negative bacilli and stimulate the growth of Gram-positive cocci. This effect is not so constant as the reverse one induced by penicillin therapy. The prolonged use of both penicillin and streptomycin simultaneously or of chlortetracycline, chloramphenicol, or oxytetracycline may suppress both Gram-positive cocci and Gram-negative bacilli to such a degree that the fungi of the yeast or mold types from the normal ecologic flora multiply and produce disease in the mouth, vagina, bronchi, lungs, and intestinal tract.[329] Vitamin deficiencies of the B-complex type, including the syndrome of pellagra, may follow the prolonged administration of the newer broad-coverage antibiotics. This view has been controverted in the recent study of Lipnik, Kligman, and Strauss,[329] of the University of Pennsylvania. These investigators found that chlortetracycline, chloramphenicol, oxytetracycline, and penicillin did not stimulate the in vitro growth of Candida albicans and also maintained that there was no clear-cut evidence of in vivo enhancement of moniliasis in mice receiving antibiotics.

SYPHILOID DISEASES

In reality, the great efforts being expended toward eradication of the treponematoses (syphilis and syphiloid diseases) should be discussed under the heading of Control, since these experiences are control on a massive scale. As stated earlier, this area of activity represents one of the really important developments in the field of syphilology (treponematoses) and the results are a tribute to the World Health Organization and the persons who have devoted themselves to the performance of this task.

Mass Treponemal Control Campaigns.—The World Health Organization * has continued its support of mass treponemal disease control programs (venereal and nonvenereal endemic syphilis, bejel, yaws, and pinta) now being developed by governments in many parts of the world. Recent advances, particularly the development in penicillin therapy, have simplified the carrying out of mass field programs. Experience has shown that this form of treatment can be readily administered on a mass basis, even in less highly developed areas, lacking many of the facilities considered essential in other parts of the world, and it is now possible to appreciate the immediate clinical as well as epidemiological value of penicillin when applied on a large scale. In the campaigns supported by WHO more than 5,000,000 persons in different parts of the world have been examined and more than 1,000,000 of these have been treated with penicillin, of which penicillin G procaine in oil with 2% aluminum monostearate (PAM) is accepted as the most practical preparation at the present time. Stress is laid on the fact that consistently good results with the simplified schedules of penicillin which are being used in these campaigns require PAM of proved characteristics which maintain effective blood levels for several days with the dosages currently employed. It has been noted that PAM preparations are varied in quality, and although these variations may not unduly upset therapeutic efficiency when multiple injections are given, they are unsuitable for mass projects, where maximum effort using a minimum amount of penicillin in one or a few injections at the smallest possible cost is the logical basis for a public

* References 330-332.

health approach. Certain international minimum specifications for repository penicillin preparations of the PAM type used in mass treponemal disease control programs have therefore been established (International Pharmacopoeia, Vol. 2). As penicillin remains one of the most expensive initial items in a treponematosis control program, the determination of the dosage to be used is an eminently practical point. Based on the recommendations of the Expert Committee on Venereal Infections and Treponematoses, a minimum dose of 1,200,000 units of PAM has been used for the treatment of early infectious lesions in adults, the minimal dose being administered on the day diagnosis is established, and, if feasible from the standpoint of field operations, a further injection may be given 3 to 5 days later. The practical effectiveness of the regimen recommended has been proved in many of the WHO-supported treponemal disease control programs, and data from the control areas in the Thailand yaws program are given by way of illustration. The success of the endemic syphilis campaign in Bosnia is also pointed out, where in three years 250,000 people in the infected areas were rid of the infection. Fifty thousand cases were treated and followed up 3 to 5 times between 1949-1952. The approach to mass treponemal disease control by penicillin therapy is one that seeks to reduce the level of infectiousness in a given area to a point where it can be successfully controlled. Mass treatment by itself is not sufficient, and it is essential that every effort should be made to strengthen the techniques of case finding to ensure that at least 90% of the population is examined. The gains obtained should be consolidated by resurveys at intervals of approximately six months to a year, when not only original cases but the entire population should be reexamined. An effective follow-up mechanism will do much to control reinfections, relapses, and the reintroduction of disease. Provided this is done, the possibility exists that the incidence of infectiousness can be reduced to a point where permanent facilities will be able to stamp out possible foci before these can spread further. Data are submitted from the various WHO-supported programs showing the value of "abortive" or preventive treatment of exposed household and other contacts (children below 15 years of age) and the necessity for maintaining "primary controlled study areas," where the patients are studied in detail with full laboratory control and follow-up procedure is outlined.

Endemic Syphilis in Bosnia: Observations and Findings in a Successful Mass Campaign.—In a monograph on endemic syphilis in Bosnia (Yugoslavia) Grin † presents studies of the natural history and control of this treponemal disease of childhood. Since 1948, the Yugoslav health administration has developed a nationwide syphilis-control program, with a special effort to control the nonvenereal endemic syphilis in Bosnia. For a number of reasons all previous control efforts have been unsuccessful, principally because no systematic examination of the entire population has been attempted, stress had been laid on the clinical and pathological rather than on the epidemiological aspects of the disease, and because of the recognized shortcomings of arsenicals for mass work in syphilis. Syphilis in Bosnia became endemic as a result of the existence over centuries of environmental conditions and epidemiological features favoring a distinct nonvenereal mode of spread. It is mainly found among the rural population but is unevently distributed over different areas, or even within an area, which may be explained by a variety of

† References 333 and 334.

factors, including social and family customs, population movements, topography, and poor communications. There are no essential differences between the clinical picture of endemic syphilis and that of sporadic venereal syphilis, but primary lesions are rare, systematic examination of large groups showing such lesions in less than 1% of the early cases; late manifestations are similar to those of sporadic venereal syphilis. Contrary to what was previously thought, investigations have shown that involvement of the central nervous system is not uncommon. Superinfection of an already infected and allergic host is considered by Grin to be the chief reason for the frequency of tertiary lesions. It was previously thought that the nonoccurrence of congenital manifestations was one of the characteristics of endemic syphilis. However, though rare, they do occur. A section of the paper deals with the organization of the field campaign, 1949-1952, emphasizing that case-finding was done by systematic serological screening of the entire population in addition to clinical investigations and that follow-up examinations included reexamining not only treated cases but the remainder of the susceptible population as well. In all, approximately 95% of the total census population of 500,000 people in endemic areas was examined, and 35,238 cases of syphilis, or 8.1% of the examined population, were treated. The use of penicillin G procaine in oil with 2% aluminum monostearate (PAM) proved decisive in the campaign. The treatment schedule for adults was generally 3,600,000 to 4,200,000 units of PAM given daily or every second day in a total of six or seven injections. Experiments were also made with single injections using smaller doses (1,500,000 units), and the results so far have been favorable. The reduction in the reservoir of infection was found to be largely dependent on the preventive treatment of household contacts. The author considers that, under favorable circumstaces, it is possible to eliminate the reservoir of infection completely within a short time by mass treatment. In less favorable conditions the disease can be checked and the reservoir reduced to a minimum over a longer period; in any case syphilis as an endemic disease in a less highly developed area can be eliminated as a public health problem; such is the case in Bosnia after a three-year campaign, now drawing to a close. The World Health Organization and the International Children's Emergency Fund have cooperated with the Yugoslav Health Administration in this program.

The International Treponematosis Laboratory Center.—Through support of WHO, Johns Hopkins University [335] established the International Treponematosis Laboratory Center, in 1950. The work has been centered on a study of the biologic characteristics of strains of treponemes isolated from patients with different clinical syndromes in various parts of the world and an investigation of the sensitivity to penicillin of strains of T. pallidum, T. pertenue, and bejel treponemes. Results have important implications, for they suggest that the basic biology of the different clinical syndromes is very similar, and what is learned about the control of one treponemal disease can probably be applied readily to another.

Rein ‡ discusses the role of the laboratory in mass treatment campaigns against yaws. Although in heavily infected population groups it is often proper to carry out mass penicillin treatment without diagnostic laboratory tests, in less heavily infected groups it is preferable to treat only those with dark-field or serologic evidence of infection. Even in heavily infected groups, the laboratory is needed

‡ References 336 and 337.

in the pilot phase of the study to determine disappearance time of the treponeme and the serologic trend following therapy, as well as to obtain a base-line picture of prevalence. Rein enumerates many gaps in our knowledge of yaws which can be filled with the help of the laboratory in the course of mass treatment campaigns.

Mass Eradication Treatment of Treponemal Diseases with Penicillin.—Rein and Kitchen [338] present the clinical and serologic results of treatment of yaws, pinta, and primary and secondary syphilis following treatment with one or a small number of injections of penicillin in an absorption-delaying medium. They point out that wide variations in the chemical and physical properties of penicillin procaine in oil with 2% aluminum monostearate have been noted in products from various regions of the world, so that the World Health Organization has set down specifications for this product which tend to insure its delayed adsorption. In patients treated for yaws with crystalline penicillin G sodium in peanut oil containing 4.8% beeswax on two- or four-day schedules, total dosage 1,200,000 to 2,400,000 units, 94 to 98% achieved clinical cure and serologic cure or improvement was noted in 92 to 94%. In patients with pinta, four schedules employing penicillin procaine in oil with 2% aluminum monostearate were compared. In the group treated with a single injection of 1,200,000 units serologic cure or improvement occurred in 73%, as compared with 72% in the group which received 300,000 units once weekly for four weeks. Primary pinta was cured in 100% of cases. In secondary pinta, there was a 69% cure rate and 31% improved. In late pinta, 40% were cured, 50% improved, and in 10% there was no change. Of patients with primary syphilis treated with a single injection of 1,200,000 or 2,400,000 units of the same penicillin preparation, 100% were seronegative at the last examination. Patients with secondary syphilis treated with 1,200,000 units achieved an 81% cure rate, and those treated with 2,400,000 units achieved a 96% cure rate. The authors conclude that a satisfactory repository penicillin preparation allows effective therapy to be administered in a single injection. This is, of course, of greatest value in those countries in which the majority of the patients must be treated by single-injection schedules in rural areas.

Bejel.—Bejel is a childhood-acquired, nonvenereal treponematosis, associated with a parasite indistinguishable from T. pallidum. It was first described in 1928, at Deir-ez-Zor, Syria, on the Euphrates, and has since been recognized at many points in the Arab world of the Near East. According to Hudson,[339] long a student of this disease, if syphilis embraces all the activities of T. pallidum in man, then bejel is endemic syphilis with an Arab flavor. Following the recent war, the Iraq government requested that the World Health Organization give advice on the treatment and control of bejel; after discussion, the World Health Organization accepted this invitation with the following modifications: The project would be shared with the United Nations International Children's Emergency Fund, because of its importance to children and pregnant mothers, and the scope of the project would be enlarged to include venereal syphilis, as well as the rural village type called bejel. The bejel-syphilis project was organized in the summer of 1950, under the auspices of WHO, UNICEF, and the Iraq government. The purpose was to treat the two forms of treponematosis in Iraq: the venereal type, as elsewhere, largely an urban problem, and the nonvenereal type known as bejel, which is a problem of rural areas. The field work started on January 1, 1951, was largely concerned with bejel. This paper is based upon the first six months' experience,

during which approximately 5,500 persons were examined and 2,477 treated. Bejel is a contagious treponematous disease of the children along the rivers, in the marshes, and in the deserts of Iraq. It occurs in household and village epidemics and seems to have a seasonal rise in the spring. Positive blood reactions among the river villagers range between 25% and 40% of the population. Positive reactions among the nomad Bedouins are probably at least 25%, and more than half of the marsh Arabs have positive reactions. The percentage of positive reactors rises with the distance from urban areas. Bejel incidence rises as the level of village hygiene falls. Symptoms, visible pathology, and positive blood reactions appear somewhat more frequently in the children and women than in men. After the childhood years, the incidence of positive reactions decreases with age, and, in a patient with positive history, the chances for a positive reaction decrease with the lapse of time since the early symptoms. Bejel is often accepted by its victims with resignation, is seldom incapacitating in its early childhood stages, and often displays long intervals of asymptomatic latency, but eventually it results in much discomfort, pain, disability, and mutilation. Penicillin injections of the repository type were given to 2,477 persons in three contrasting and widely separated areas of Iraq. One injection of 600,000 units in infants and from 1,200,000 to 1,800,000 units in children and adults is sufficient to heal early lesions and heal or ameliorate late lesions. It is not assumed that these dosages cure the patients or reverse the reactions. Within a few years, bejel can be controlled and virtually eliminated by a program of small medical teams, using only penicillin and circulating along definite routes, traversed again at annual intervals. This program would be accelerated by any activity aimed at improvement of village hygiene and welfare. This paper represents a preliminary report, based upon the experience of the first six months, when the project was just getting under way. Since WHO and UNICEF are both continuing their interest in this project, more and fuller information, doubtless, will be made available from time to time. Chaglassian and co-workers [340] found that the prevalence of treponematosis among the tribesmen around Badana, Saudi Arabia, is 37.8% out of a sample of 81 unselected cases. On the whole, the clinical picture is similar to that of syphilis and bejel as reported by Hudson, Hasselman, and Akrawi and as seen by Chaglassian in the Deir-ez-Zor district. The majority of cases had acquired the disease in childhood, but some acquired it later in life. Possibly the majority had acquired it nonvenereally, but venereal contacts could not be disregarded. It is realized that the group screened is small and statistical error is likely. However, the prevalence of treponematosis is high. Saudi Arabia constitutes a reservoir of infection with possibility of transfer to other areas. The clinical picture, incidence, and laboratory findings paralleled Hudson's study of similar tribes in Iraq (1951). Csonka § has reported that during the year of 1951 about 6,000 bejel patients were treated by WHO teams, 10,000 serums were tested, and 15,000 people were examined. Bejel has its greatest incidence in the primitive village settlements. The country is marshy in the south. Most foci were found near water in the remote villages, little or none in the mountains, and comparatively little in the desert communities. The most encouraging single feature was the sharp decline of new infectious cases. Although penicillin is proving efficient in controlling bejel, the most permanent safeguard will be a raising of hygienic standards.

§ References 341 and 342.

Pinta.—In a series of four papers, Edmundson, Rico, and Olansky [343] report their findings in studies of pinta in a number of communities in the Tepalcatepec Basin, in Mexico. Because of the unwillingness of patients in this area to undress, clinical examination was confined to examination of the exposed skin areas. It was found that the diagnosis could be made with a high degree of accuracy by examining only the exposed skin surfaces. In one series, self-diagnosis by the patient was found to be accurate in most cases. There was a high degree of correlation between clinical diagnosis of pinta and seroreaction. Persons with no clinical evidence of pinta who were seropositive were considered to have syphilis, to have had previous treatment for pinta, to have been misdiagnosed, or to be biologic-false-positive reactors. However, there was no evidence of a high incidence of biologic false positivity. Latent pinta (seropositive untreated patients without clinical evidence of disease) was thought to be either nonexistent or extremely uncommon. In two communities in which many patients had previously been treated, pinta was found to be disappearing, as evidenced by the relatively few children found infected. Titered serologic tests in pinta were relatively constant, the mean VDRL titer being 32 units, the mean Kahn titer, 128 units. Titer tended to remain at a constant level regardless of the age of the patient and the duration of the disease. The authors conclude that serologic examinations are not necessary or practical as a case-finding device in mass surveys for pinta. Adequate treatment of clinical cases, vigilance for and prompt treatment of newly infected patients appearing or arriving in the treated area, and prompt retreatment of relapsing cases offer a practical and economical approach to the control of this disease. Pinta too has yielded to penicillin therapy. Kitchen and his co-workers || report that, based on clinical response, repository penicillin (microscrystalline penicillin G procaine in oil and aluminum monostearate) is the drug of choice in the present-day treatment of pinta. This report is based on 655 patients with pinta treated with four schedules of penicillin therapy. Blood specimens were collected from each patient for serologic examinations prior to treatment. Three hundred fifty patients were available for clinical and serologic reexamination at varying intervals up to two years after completion of therapy. The clinical results with penicillin therapy were exceptionally good and far superior to any other form of therapy ever employed, including heavy metals, chlortetracycline, chloramphenicol, and streptomycin. Serologic results are also presented. The cause of pinta is known, and an effective ambulatory single-injection schedule has been established. Eradication of this disfiguring and stigmatizing disease now looms as a distinct possibility

Yaws.—The progress in the fight against yaws has been so striking as to excite editorial comment in the New England Journal of Medicine.[346] It is significant that, in spite of the tremendous size of the problem, up to the end of December, 1952, nearly 8,000,000 persons have been examined in Haiti,[347] Indonesia, Thailand, and the Philippines,¶ in the course of large-scale campaigns against yaws with the assistance of WHO. It has been calculated that the cost of the treatment given, including expenditure for staff and materials, amounts to less than $3.00 per capita. The Inter-American Cooperative Health Service [350] has also been active in this field,

|| References 344 and 345.

¶ References 348 and 349.

and an informal statement is presented of the work accomplished in Yaws control in Columbia. With respect to drugs used in the therapy of yaws, penicillin holds the fore,# but chloramphenicol [353] as well as oxytetracycline have been used.[354]

Nomenclature in Yaws.—Hasselmann [355] makes a plea for accurate and concise terminology to be employed in the mass campaigns against yaws initiated by the United Nations World Health Organization on an international basis in Haiti, Indonesia, Malaya, the Philippine Islands, and Thailand. Hasselmann points out how unreasonable and illogical it is to refer in frambesia to "primary," "secondary," or "tertiary" lesions and stages as in syphilis, inasmuch as the initial "primary" yaw may persist throughout the entire subsequent stage of generalized metastatic polypapillomata, corresponding to secondary syphilis. In frambesiology, it appears sufficiently descriptive to refer to the lesions as (*a*) initial yaw, whether papular or already papillomatous; (*b*) generalized, metastatic papules and mostly papillomata (polypapillomatous stage); (*c*) the late stage, with (1) keratodermia of soles and/or palms and (2) ulcerative lesions, wherever these are located and irrespective of their indeterminable pathogenesis, except in experimental frambesia.

Yaws and Flies.—On the basis of the literature and a questionnaire, Barnard [356] found that various species of flies can and do act as mechanical vectors of yaws in most parts of the tropics, but the extent to which this is an important or even common mode of dissemination is uncertain and probably varies in different localities.

CONTROL OF SYPHILIS

Public Health Problems in Syphilis Control.—According to Bauer,* three factors seem to stand out in surveying the present venereal disease control problem. 1. The venereal disease control program becomes more and more one of finding and treating persons with latent and late stages of syphilis in order to prevent disability and premature death. 2. Outpatient treatment will characterize treatment activities in the future. This fact, without any planning impetus from health agencies, brings the private physician into the control picture in a very responsible position. 3. In order to serve the private physician competently in the coming years, it will be necessary for health departments to provide him, if he wishes, with contact interview and investigative skills. In addition to that it will be important for the medical schools throughout the country to alert their undergraduate and graduate students to the essential role of the private physician in the continuing venereal disease control program. It will also be important that these medical students, soon to embark on careers in American communities, be familiar with the services their health departments have to offer them in meeting their responsibility in venereal disease control.

Adjusting Venereal Disease Control to the Antibiotic Era.—In his presidential address before the American Venereal Disease Association, in May, 1950, Sternberg [359] decries the trend toward deemphasis of venereal disease control, stating that "it would be foolish, indeed, to send the firemen home because the brightness of the flame has dimmed." The still considerable number of cases of infectious syphilis in this country provides a focus of infection which could be fanned to nation-wide dimensions if our venereal disease control efforts should lessen or if

References 351 and 352.

* References 357 and 358.

a national catastrophe should occur. In addition, viewing the problem as a global one, there is urgent need for more, rather than less, effort in the war against the treponematoses. Young qualified physicians must be attracted to this field, and our fundamental knowledge of the disease must be increased. Many problems in treatment remain unsolved. This is the time for expanding rather than contracting our efforts against the venereal diseases.

The Economics of Venereal Disease Control.—The Lederle Bulletin,[360] in a well-illustrated public service summary, points out that the incidence of gonorrhea continues to be high and the incidence of syphilis continues to be substantial in the civilian population of the United States. The length of hospitalization required for the treatment of these venereal diseases has been sharply reduced by modern penicillin therapy, but nonetheless it constitutes a very considerable economic loss both in man-years and in dollar expenditures. The decrease in morbidity is encouraging, but past experience has shown that it may be evanescent. The continual population exchange permitted by modern transportation facilities makes new epidemics possible as long as an endemic focus exists. Long-term trends, quite apart from the use of such innovations as the antibiotics, appear to be in the direction of decreasing incidence of syphilis. Relegation of syphilis to the minor status now shared by such diseases as diphtheria and smallpox is still in the wishful-thinking stage. All methods of control and early therapy must continue to be used. On the whole, it would appear, however, that syphilis in the United States is rapidly yielding to a combination of technologic skills and improving socioeconomic environment. The costs of syphilis have not recently been the subject of specific appraisal. It would be interesting to compare the present-day figures with those obtained from the literature in the prepenicillin era by Beerman.[361]

Other general summaries on syphilis control include that of Gayoso [362] and Zoon and Van Steenbergen.[363] Case-finding by annual examination † and medical examination of prostitutes [366] have all yielded dividends. Certain screening methods employed by the Cumberland County, N. C., Health Department for case-finding [367] may be adapted to most local health departments. An eight-month period of selective screening of small industrial plants proved to be a diversified, yet highly profitable, screening method. About 17% of those tested were reactors. Employing the State venereal disease survey team, large industrial plants were screened in an 11-day period, and approximately 12% of those tested were reactors.

Health certification during the year screened 5,190 examinees who professed negative serologic tests prior to examination. About 5% were found to be reactors. By screening a total of 9,093 persons from a population of 65,000 (aged 15 to 70), 738 reactors were found. In other words, by careful screening of 14% of the population, 39% of the estimated total reactors in the county were found. Disposition of the positive serologic tests found in the industrial surveys indicated a majority of late latent and tertiary cases of syphilis in the older age groups. A significant percentage of early latent syphilis was found, however. Screening by health certification is an effective method of finding early cases of syphilis, as the examinees for the most part represent a high-incidence group prone to reinfection. The effect of marital instability, promiscuity, and antisocial behavior on the acqui-

† References 364 and 365.

sition of venereal disease is offered as a basis for selecting groups in the population for survey. Antisocial behavior, particularly, may help to explain the differences in rates between Negroes and whites.

Of 1,935 contacts reported after investigation as noninfected, 266, or 13.7%, were subsequently reported by Sklar, Schuman, and Rose [368] as having become infected with syphilis or gonorrhea. Of these, 198, or 10.2%, of the contacts initially investigated were found infected sometime after the conclusion of the initial investigation. Syphilis cases reported in this group totaled 90, or 4.6%, of all noninfected contacts. Early infectious (primary and secondary) syphilis totaled 53 cases, or 58.9% of all cases of syphilis subsequently reported. The majority of all venereal disease cases subsequently reported among such "noninfected" contacts were reported within one year after the initial investigation. The spontaneity of this reporting is emphasized and references drawn as to yield after reexamination of the noninfected contact reservoir. Voluntary reporting of venereal diseases by reporting agencies to the venereal disease central registry in the Illinois Department of Public Health has been utilized in this study to pinpoint administratively the need for further control measures in the follow-up of contacts to primary and secondary cases of syphilis, who, upon their initial examination and investigation, were found to be noninfected with a venereal disease.

Venereal Disease Contact Investigation: A Combined Military-Civilian Program.—Fiumara, Segal, and Jolly [369] summarized the basic principles of a military venereal disease control program. It emphasizes that adequate control measures must have complementary action on the part of civilian authorities. They further described the unique experiences of the Massachusetts Health Department not only in interviewing military patients for contacts but also in engaging the military hospital corpsmen in the highly specialized art of contact interviewing. The study points out the need for highly trained personnel in carrying out contact interviewing by comparing the results of interviewing by relatively untrained versus trained people. The hospital corpsmen, who have had little training in interviewing, were able to obtain 1.13 contacts per patient with gonorrhea and 1.58 contacts per patient with syphilis. In contrast, the nurses obtained 1.29 contacts for gonorrhea and 3.46 contacts for syphilis. With the information supplied by the military interviewers, civilian health departments were able to locate 34.1% of the gonorrheal contacts and 52.6% of the syphilis contacts. On the other hand, information supplied by the nurses resulted in 43.2% of the gonorrheal contacts and 42.2% of the syphilis contacts being found. Of striking importance was the epidemiological index. From information supplied by the hospital corpsman, the epidemiological index was 0.33 for gonorrhea and 0.17 for syphilis. In contrast, the epidemiological indexes from information supplied by the nurses were 0.47 for gonorrhea and 0.38 for syphilis. One of the important points brought out in this study is the obvious necessity for the states to improve their contact-investigation activities.

Results of Investigation of Contacts Reported by Military Services.—An analysis of the results of contact investigation of 714 military venereal disease patients in Massachusetts in 1951 by Fiumara [370] reveals that 70% of the contacts were reported to be pickups and only 7.5% prostitutes. Ninety-seven percent of the contacts were encountered through efforts of the patients without assistance by a third party. Sixty percent of the encounters were in restaurants, bars, or taverns. About one-third of the exposures took place in a home, about one-fourth in a hotel, and about

one-fifth in an automobile. Of the 781 contacts named 24% were completely identified by the patient. With complete information 82% of the contacts were found and examined, whereas with incomplete information only 50% were located. Reinterview, when information was inadequate, resulted in finding an additional 13% of the contacts. A plea is made to improve the caliber of contact interviews, since more than 75% of the contact information was found to be incomplete.

A picture of the venereal disease problem in the armed forces in the Far East during the first year of the Korean War is presented by Graham.[371] Of the total of 15,000 cases of venereal disease reported in the naval forces during 1951, 10,000 were gonorrhea, only 147 syphilis, and almost 5,000 chancroid. In Japan prostitution has increased tremendously since World War II. In some port cities as high as one-tenth of the population is employed directly or indirectly in prostitution. Inadequate laws regulate venereal disease control and prostitution in most cities. Until the present time, there have been poor civilian contact investigation and poor diagnostic laboratory facilities. Through the help of Naval Venereal Disease Control Officers some of these deficits are being remedied, and with increased emphasis on morale building in the Armed Services it is hoped and expected that the venereal disease attack rate will be lowered.

Serological Aspects of a Syphilis-Control Program in the Ghund Area.—Reports ‡ on a WHO project for mass treatment of syphilis among a limited population were recently published. Although limited in scope by the uncooperative attitude of the population in the Ghund area, Himachal Pradesh, India, the serologic results clearly demonstrate a decrease in seropositivity one year after treatment, which indicates that the administration of repository penicillin significantly reduced the reservoir of infection.

Blood Testing for Syphilis in an Island Population.—Moorhead and his coworkers [374] report upon a project, undertaken by the United States Public Health Service, in which over a 60-day period 48% of the population of the Virgin Islands were given serologic test for syphilis. Seventeen percent of the Negro population, 2.3% of the white population, and 7.9% of the mixed and other races were found seroreactive. Significant differences were found for Negroes on the three different islands in which the project was carried out. Seropositivity rates for immigrants, who were mostly Negroes coming to stay on St. Thomas for a few days or weeks, were significantly higher than for the permanent population. It was estimated that for each case of syphilis found and treated by means of the survey there remained two undiscovered cases in need of treatment.

Location of Testing Stations in a Mass Survey.—Stuart, Davis, and Jolly [375] analyzed the effectiveness of various types of serologic testing stations utilized in Atlanta, Ga., in the course of a multiple health-testing survey in which 40% of the population, 235,000 people, were tested in a period of 76 days. Analysis was based both on the number of persons applying to the individual stations and on the percentage of positive serologic tests discovered. Stations open to the public included health centers, stores, schools, and churches. Stations not serving the general public included prisons, manufacturing and utility plants, governmental and other offices, and schools and colleges. The most successful station was "Under the Viaduct" where 32.5% of almost 15,000 serologic tests were positive or doubtful. "Under the

‡ References 372 and 373.

Viaduct" was in the heart of the downtown Negro area. Popular piano music, drawings for prizes, live radio programs, free soft drinks, and recruitment of persons to be tested by voluntary personnel in the community contributed to the success of this station. White schools and churches were found to be definitely inferior to Negro schools and churches from the point of view of case-finding. Prisons and a permanent downtown clinic were found to be good sources of syphilis suspects. The authors present many practical suggestions regarding the location of testing stations in mass surveys.

Gonorrhea and Syphilis in Marital Partners.—Keldbeck and Marcussen [376] found that in marital partners the spread of gonorrhea to both partners occurred in a higher percentage than did the spread of syphilis. The male partner was the prevailing source of infection with gonorrhea, contracted from a single coitus with unknown partner, while the female partner often was the source of infection with syphilis, contracted from steadier extramarital partnership.

Alcohol and Venereal Disease.—The committee appointed under government auspices to investigate problems concerned with the control of alcohol in Sweden [377] made a special study of the connection between alcohol and venereal disease. Over 1,400 questionnaires were answered well enough to be suitable for statistical study. Infections received on Saturdays and Sundays were more numerous than during the rest of the week. Nearly half the seamen were infected by prostitutes, and about four-fifths of the men infected by prostitutes were under the influence of alcohol at the time. During casual relationships more than half the men were under the influence of alcohol, and 42% of the women with casual partners consumed alcohol at the time. Patients infected abroad were more often under the influence of alcohol at the time than patients infected in Sweden.

Occurrence of Venereal Disease in Cases of Well-Educated Persons.—In a study conducted by Marcussen [378] among the students in Denmark, it was found that about 0.92% of those at the University of Copenhagen yearly seek examination for venereal disease. For all occupational groups, age 15 to 39 years the figure was 2.84%. Of the students, 0.36% had a new infection, while in the other group 2.08% had new infections. Special instruction concerning the venereal diseases provided by the University for the students probably accounted for the difference.

Influence of Sexual Habits on the Epidemic Curves of Syphilis and Gonorrhea.—Marcussen [379] noted that in Copenhagen the peak of the epidemic curve of syphilis in 1945 was seven times the normal value, while the peak of the epidemic curve of gonorrhea was only three times the normal value. This may be explained by the relative surplus of female patients when the epidemic was at its maximum. Female patients proved to have a high proportion of steady sexual contacts at the height of the epidemic, and most likely this favored the infection with syphilis more than the spreading of gonorrhea.

Congenital Syphilis: Incidence at the Boston City Hospital.—In a survey covering the period from June 1, 1951, to Oct. 21, 1951, Fiumara and his co-workers [380] found that 1,005 women were delivered and studied serologically for syphilis at the Boston City Hospital within 48 hours of delivery. Twenty-four were found to have been infected with syphilis. The mean age of the mothers was 26.7 years, an average that was not materially affected by race or marital status. Four percent were single. A little more than 72% of the mothers were white; 2.9% of these were single,

whereas 7.7% of the Negro mothers were single. About a quarter of the cases had no prenatal care. Eight (33.3%) of the 24 mothers found to have syphilis were in this group. Of the mothers who had prenatal care about half (51.7%) consulted a physician for the first time at the third trimester, 40.2% at the second, and only 8.1% at the first trimester. This pattern of late prenatal care was independent of the racial, marital, or parous status of the patients. Fewer than half of the 24 mothers ultimately found to be infected had their disease diagnosed during the prenatal period. In nearly all the diagnosis would have been made prenatally if they had had prenatal care. In the group the total syphilis rate (old and new cases) was 2.4% but the incidence of newly discovered syphilis was 1.1%. Twice as many Negro as white women were found to be infected. There were no multiple births in this series, but 119 (11.8%) of the babies were born prematurely. The prematurity rate was twice as high in the patients with recently diagnosed syphilis as in the nonsyphilitic group. No cases of congenital syphilis were found in this series. An interesting sidelight of the study was the fact that the blood test for syphilis was not adversely affected by anesthesia.

Porter [381] has reviewed a recent study of the congenital syphilis problem in Delaware. The study was conducted along two lines, a survey of all cases currently under observation being coupled with an attempt to discover new cases. As a result of this study, the following conclusions were made: 1. The static incidence of reported cases of congenital syphilis does not reflect failure of present recommended treatment for the pregnant woman with syphilis. 2. The picture would improve if the best knowledge and facilities available were applied. 3. Repeating the serologic test in late pregnancy is a desirable practice. 4. Intensive search for new cases of congenital syphilis in children has been relatively unproductive. 5. Most reported new cases are adults who are already aware of their disease. 6. Diagnosis of syphilis in infants presents problems that require much consideration and effort, as many uninfected infants needlessly are treated for syphilis.

Wright and his colleagues [382] summarize a study of the congenital syphilis problem made by the North Carolina Syphilis Studies in the area surrounding Chapel Hill and Durham, N. C. A series of 60 cases of congenital syphilis recently brought to treatment in a four-county area in North Carolina was studied intensively in retrospect, the object being to learn why these cases had not been prevented and why they had not been treated more promptly. All available information on the health and medical care received by each of the 54 families between the known or assumed onset of the mother's infection and the final discovery of the syphilitic child was studied and was compared with the services which they would have received had it been possible to carry out the theoretical program to perfection. As a result of this study, 348 specific opportunities were found which, had care been ideal, would have resulted in prevention or adequate treatment of the congenital infections. The most frequent deficiencies had been in detecting syphilis of parent or child, in carrying out family-contact investigations, in carrying out follow-up, in getting the cooperation of families in following advice, and in rendering an integrated type of health care to families. Several brief case reports are presented illustrating various ways in which control opportunities were missed. Another study [383] was made of the extent and pattern of use of the prenatal serologic test for syphilis in Orange, Person, and Chatham Counties, N. C., during the period 1941-1949. The method of study was to match serologic test reports from labora-

tories against the birth certificates. Despite the prenatal law, effective in the State since 1940, serologic tests have been performed in only 54% of 16,017 pregnancies during the nine-year period. The study has demonstrated that it is not safe to assume that all pregnant women received blood tests merely because the law required such tests. An evaluation of the extent of prenatal testing should be a part of the total syphilis control program in each community, and the evaluation should be used as a part of professional education designed to supplement the effectiveness of the prenatal law. Gifford and her colleagues [384] point out the many opportunities the public health nurse has to help eliminate congenital syphilis. These opportunities lie in the areas of detection, prevention, case-finding, follow-up, and treatment.

Obstacles to Eradicating Congenital Syphilis.—At present, about 13,000 cases of congenital syphilis are reported each year in the continental United States, and it is estimated that there is a residue of 100,000 undiscovered cases in our child population, ages 0 to 10 years. According to Wright and his co-workers,[385] during 1941-1949 one-half of all cases were reported from 13 southern states, which together include only about one-fourth of the total population. The total number of reported cases has remained constant since 1944. This could be accounted for by the success of the case-finding program among older children. But in some communities it is possible that the residue of undiscovered cases is being at least partially replenished by significant numbers of syphilitic newborn infants, few of whom have their condition diagnosed in infancy. The North Carolina Syphilis Studies has developed a simple classification of the types of opportunities which professional health workers have for bringing about the eradication of congenital syphilis. Control opportunities are classified into five types: detection, prevention, contact-tracing, treatment, and follow-up. This classification was used in the study of 60 cases of congenital syphilis discovered in from North Carolina counties during the period 1946-1950. Ages of the 60 patients at the time of final discovery ranged from 1 month to 24 years, with a median age of 8 years. Their histories demonstrate weaknesses of control programs in years past. Altogether, for the 60 cases studied, 34 missed control opportunities were identified. The least number for any case was 1; the greatest number was 18. This Tabulation presents the number and relative frequency with which each type of control opportunity had been missed.

Types of Control Opportunity	No.	%
Detection opportunities	199	57.2
Prevention opportunities	12	3.4
Contact-tracing opportunities	85	24.4
Follow-up opportunities	46	13.2
Treatment opportunities	6	1.7

Some detection opportunities had been overlooked because mothers were allowed to go through pregnancy and delivery without a serologic test for syphilis having been done. In North Carolina a prenatal-blood-test law went into effect in January, 1940. Yet a study of over 16,000 pregnancies occurring in three North Carolina counties during 1941-1949 showed that a serologic test for syphilis had been done during pregnancy or at the time of delivery in only 54% of pregnancies. Another significant cause of missed detection opportunities was the division of responsibilities among different professional workers who were not in close communication. The needed records (containing data on previous diagnosis or suspicion of syphilis in the family) were in other departments of the same agency or in other

agencies or offices. Follow-up opportunities also were lost because the health care of the family was not integrated. Even the health care of the individual was often a series of separate episodes, because useful information was scattered among agencies and professional persons who were not in communication.

To eradicate congenital syphilis more emphasis is needed on the following activities: (1) making the initial step of detecting a case of syphilis in a family; (2) following the chain of infection until all infected family members are located; (3) keeping the family under observation until the possibility of future congenital infections is eliminated and any child already infected is treated.

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Case Reports

OCCURRENCE OF SECONDARY HEMOCHROMATOSIS IN PATIENT WITH THALASSEMIA MAJOR

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IDIOPATHIC hemochromatosis was first described by Hartman and Chausser, in 1882. They described the classic tetrad of liver disease, diabetes, pigmentation of the skin, and atrophy of the gonads. Howard and Stevens, in 1917, were among the first to demonstrate that abnormal iron metabolism was the basis of this condition. What abnormality in iron metabolism leads to hemochromatosis has only recently been elicited.

In 1937 a closely related disease following repeated blood transfusions was described by Kark. Since that time numerous observers have reported the occurrence of hemosiderin deposits in the liver and other organs following blood transfusions. Several of the reports, notably those of Mackey, of Aufderheide, Horns, and Goldish, and of Chesner, also have shown cirrhosis of the liver to be a further complication. Other instances of this condition have been reported after prolonged oral administration of iron salts. Goldish and Aufderheide pointed out that there is often more iron pigment in the liver cells than can be accounted for by the number of transfusions these patients received. This fact led them to postulate an abnormally increased iron absorption from the gastrointestinal tract as a factor in the pathogenesis of this exogenous type of hemochromatosis.

Thalassemia has been believed by many observers to represent a hereditary defect in iron metabolism and incorporation of the metal into the red blood cell. Whipple and Bradford commented on the pathological relationship of this disease to idiopathic hemochromatosis in 1932. Mallory, in 1935, stated that this "disease is hemochromatosis of children." So few patients with thalassemia major live to adult life that the complications of this increased iron deposition in the tissues and particularly in the liver are of little clinical importance. The following case is of interest not only because of the severity of the liver disease associated with abnormal iron deposition but also because of the length of the patient's survival.

REPORT OF A CASE

A 25-year-old Italian woman was admitted to the medical service of the Long Island College Hospital, on Sept. 15, 1953, complaining of ankle and facial edema and swelling of the abdomen of two weeks' duration.

The patient had first been seen at the Long Island College Hospital in 1933, when a diagnosis of thalassemia had been made. At that time the hemoglobin was 7 gm. and the red blood cell count was 2,500,000. A splenectomy was performed, and the patient was followed in the Pediatrics Clinic, receiving blood transfusions at infrequent intervals. In 1944 the patient was admitted to

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the Medical Service for evaluation. The previous diagnosis was confirmed. The only pertinent finding on physical examination at that time was that the liver was palpable 4 fingerbreadths below the right costal margin. Blood studies revealed a hemoglobin of 6 gm., red blood cell count of 2,000,000, and white blood cell count of 14,000, with many normoblasts on blood smear as well as target cells and red blood cells of bizarre shapes. There was increased resistance of the red blood cells to osmotic pressure. The reticulocyte count was increased, and the bone marrow revealed erythroid hyperplasia. Roentgen examination of the bones revealed changes compatible with thalassemia. At this time the patient received four blood transfusions of 500 cc. each.

Laboratory Data

	9/16/53	9/20/53	
Hemoglobin	7 gm.	6.5 gm.	
Red blood cells	2,760,000	2,560,000	
White blood cells*	23,390	35,994	
Neutrophiles	55	65	
Lymphocytes	37	27	
Monocytes	6	2	
Eosinophiles	2	4	
Reticulocytes	6.4%		
Fragility, osmotic	Control: begin 0.46%, complete 0.36% Patient: begin 0.46%, complete 0.32%		
Bleeding time	5 min.		
Clotting time (Lee-White)	4 min., 30 sec.		
Clot retraction	1 hr.		
Platelet count	620,000		
Urine			
Specific gravity	1.006		
Albumin	2+		
Sugar	0		
Acetone	0		
Microscopic examination	Rare white blood cells		
Fishberg concentration test	1.008	1.008	1.010
Phenolsulfonphthalein excretion	80% in 2 hr.		
Blood sugar, mg./100 cc.	70		
Urea, mg./100 cc.	40		
Total protein, gm./100 cc.	7.0		6.4
Serum albumin, gm./100 cc.	2.9		2.5
Serum globulin, gm./100 cc.	4.1		3.9
Cholesterol, mg./100 cc.	110		122
Cholesterol esters, mg./100 cc.	52		Trace
Icterus index	21		
Thymol turbidity	5.3 units		
Cephalin flocculation	4+, 48 hr.		
Prothrombin time	Patient, 19 sec.; control, 17 sec.		
Sulfobromophthalein retention	15%, 45 min.		
Lupus preparation	Negative		
Electrocardiogram	Normal		
Chest roentgenogram	Normal		
Roentgenogram of skull	Demineralization of the bones of the skull and cervical spine, with exaggeration of the diploic markings		

* Majority of white blood cells are normoblasts.

After discharge the patient failed to return to Clinic and received no therapy of any type until January, 1950. At that time she was readmitted to the Medical Service, complaining of repeated episodes of right upper quadrant pain and a deepening jaundice. Examination at that time again confirmed the diagnosis of thalassemia major. Roentgen examination of the abdomen revealed the presence of laminated stones in the right upper quadrant. A cholecystectomy and common duct exploration revealed the presence of numerous calcium bilirubinate stones in the gallbladder and common duct. Following this procedure the icterus returned to its previous levels. The patient at this time received six blood transfusions.

The patient was discharged in March, 1950, but returned in May with homologous serum jaundice. She had a very severe illness and was in coma for three days. Finally a favorable

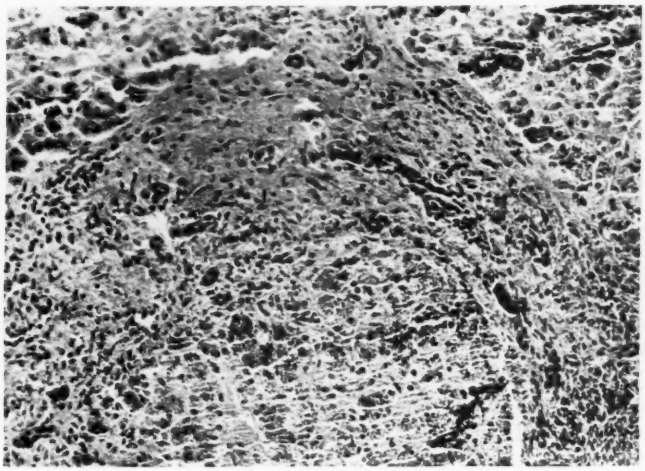

Fig. 1.—Liver, showing pseudolobulation of liver tissue; Hematoxylin and eosin stain. There is increased amount of fibrous tissue and proliferation of the surrounding bile ducts. The liver cells show many fine pigment granules.

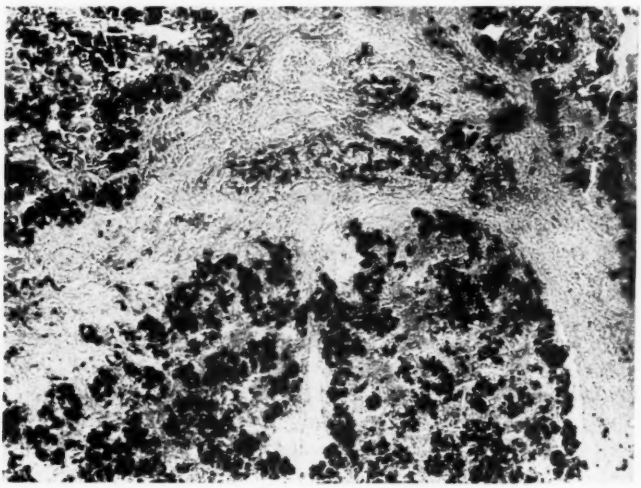

Fig. 2.—Iron stain of the same tissue, showing large amounts of hemosiderin deposits in the liver parenchyma.

response to therapy was obtained, and she was discharged in July, 1950. She remained well and asymptomatic, save for a brief episode of pneumonia, until September, 1953. During all this time the patient refused transfusion therapy, stating that she "felt well."

On Sept. 1, 1953, the patient noted on awakening that her eyes were swollen. The swelling disappeared during the day, but by evening the ankles were also edematous. At the same time she noted progressive swelling of the abdomen. The appetite remained excellent, and she had no other complaints. She was admitted to the hospital on Sept. 15, 1953, for further evaluation.

Admission physical examination revealed a young Italian woman of stated age in no acute distress, weighing 139 lb. (62.5 kg.). The temperature was 99.2 F.; pulse rate, 86; respiration rate, 16, and blood pressure, 138/80.

The skin was light green. The sclerae were slightly icteric. The head and neck were normal. The lungs were clear to percussion and auscultation. The heart was not enlarged to percussion, but a Grade III systolic murmur was present at the apex. The abdomen was distended. The liver was palpable 4 fingerbreadths below the costal margin. There were well-healed scars in the left and right upper quadrants. There was shifting dullness in the abdomen, and a fluid wave could be elicited. There was edema of both ankles, with pretibial edema.

The laboratory data are shown in the Table.

On Sept. 20, 1953, a liver biopsy was performed (Figs. 1 and 2).

The patient was treated with a high-protein low-sodium diet with weekly mercurial injections. She lost 25 lb. (11.3 kg.) and was discharged asymptomatic and edema-free three weeks after admission.

COMMENT

This case is unusual in several respects. Very few patients with thalassemia major live to adult life. March, Schlyen, and Schwartz found 26 adult cases in a review of the literature. Certainly other cases have occurred, but survival into adult life with the severe lethal form of the disease is unusual.

This case also demonstrates the close relationship of this disease to iron metabolism. For years observers have noted hemosiderosis at autopsy of these patients. While Mediterranean anemia is not characterized by hemolytic crises, as are spherocytosis and sickle cell disease, the work of Crosby and Ackeroy has shown the average life span of red blood cells to be shortened. They average 20 to 30 days, in contradistinction to the normal life span, of 120 days. As a consequence, excess amounts of iron pigments occur in the tissues. However, often more iron pigment is found than can be accounted for by red blood cell destruction.

Studies of iron metabolism show that there is no method of adequate removal of iron from the tissues. The level of iron in the body is apparently controlled by regulating its absorption from the upper gastrointestinal tract. The iron is absorbed and stored as ferritin in the gastrointestinal mucosa. From there it enters the blood stream in relation to the body's need. It is transported to storage depots as transferrin; one molecule of the protein is able to bind two atoms of iron. From the storage depots iron is used in the cytochrome system as well as in red blood cell formation. Slight amounts of iron are removed in the bile and via the skin, but the amounts removed in this fashion are negligible. Therefore, anything increasing iron absorption will lead to deposits of iron in the tissues and, especially, the liver. In thalassemia, it has been postulated that iron is absorbed in excess of the body's ability to metabolize it and saturates the tissues.

Increased amounts of iron pigment in the tissues after a period of years lead to degenerative changes in the affected organ. As the liver is the organ primarily involved, the result is cirrhosis of that organ.

Recent work of Peterson and Ettinger and of Dubach, Callender, and Moore with radioactive iron has shown the major defect in idiopathic hemochromatosis to be increased absorption of iron from the gastrointestinal tract. Gillman and Gillman have shown that a low-phosphorus diet, as ingested by the natives in Africa, leads to increased iron absorption and, eventually, severe liver disease, as noted above. It is probable that a similarly increased iron absorption is associated with thalassemia and is the primary factor in the pathogenesis of the associated hemochromatosis.

This patient now presents the clinical picture of severe liver disease, and the symptoms are directly attributable to this condition. The liver disease probably represents the end-result of the previous homologous serum jaundice and is being exaggerated by the excess deposition of iron pigment, as shown by liver biopsy. However, save for six transfusions at the time of the cholecystectomy and four transfusions 10 years ago this patient has had no other transfusions for 10 years. Therefore, the excess iron pigment represents the end-result of her own red blood cell destruction and also increased absorption from the gastrointestinal tract and is not as a result of transfusion therapy.

In recent years big strides have been made in transfusion therapy for thalassemia. It is likely, therefore, that increasing numbers of patients with the severe form of this disease will survive to adult life. They will be increasingly prone to develop hemochromatosis, both from transfusions and from the basic altered metabolism of their disease.

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OCCURRENCE OF ASCITES IN MYXEDEMA

Report of Two Cases

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> Anasarca to a slight degree was not uncommon though in no instance was it excessive. On the other hand, passive effusions into serous cavities, sometimes to a considerable amount, were frequently noted.

ALTHOUGH this quotation dates back to a report of a Committee of the Clinical Society of London nominated in 1883 to investigate the subject of myxedema,[1] nevertheless, the reports of a combination of myxedema and ascites since that time are infrequent. Watson and associates [2] reported that only 22 well-established cases of myxedema with ascites had been recorded prior to 1941. While the recognition of a typical case of myxedema should not be difficult, actually some confusion may be encountered, especially when there are findings of serous effusions, dyspnea, and a great amount of pitting edema. McGavack [3] notes that a number of such cases are admitted to hospitals as cardiac cases. Ascites in such a patient requires the exclusion of other diseases, including congestive heart failure, before it can logically be considered an integral part of the myxedema picture. In this regard it may be similar to the pericardial effusion in myxedema. Ascites, however, is considered an infrequent occurrence, whereas, according to Kern and associates,[4] pericardial effusion is a more or less constant part of myxedema.

The response of myxedematous patients to appropriate therapy is frequently gratifying. The cases herein reported are discussed from the standpoint of diagnosis and management.

REPORT OF CASES

CASE 1.—H. F., a 44-year-old white man, discharged from the Army in 1946, obtained work which required only a moderate amount of physical exertion. Within three months he became physically incapable of continuing this work. His voice gradually became deeper. While doing minimal work about his home he noticed increasing fatigue. Between 1946 and 1952 he lost his pubic and axillary hair and developed a rough dry skin. In addition, his memory became poor and he noticed loss of libido. Six months prior to admission to the hospital his legs and abdomen swelled and he noted progressive shortness of breath. Eventually he found it difficult to get out of a chair. Stairs had to be ascended one step at a time. He finally became semistuporous, and he slept for long periods, usually in a sitting position. Later, shortness of breath became so alarming that he was persuaded to enter the Veterans Administration Hospital, Hines, Ill., on April 14, 1952.

Physical examination revealed a well-developed obese-appearing white man with a very deep husky voice, a remarkably dry skin, and complete alopecia. Dyspnea was severe. There were

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The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

a few small cervical lymph nodes palpable. The outer aspect of his eyebrows was missing; there was a purulent conjunctivitis on the left and a periorbital edema bilaterally. The tongue was large and smooth. Dullness was noted in both lung bases, and on auscultation dry rales were heard over these areas. On percussion the cardiac dullness extended to the anterior axillary line. This finding was supported by a portable chest x-ray showing the heart to be markedly enlarged (Fig. 1). The cardiac rhythm was regular, the rate 52 beats per minute. The heart sounds were of poor quality. There were no murmurs. The blood pressure was 100/80. The abdomen was greatly distended with fluid (Fig. 2). No masses could be palpated. An umbilical hernia was present. The genitalia were edematous; pubic and axillary hair was absent, and there was a 4 + pitting edema of the lower extremities.

On admission the patient was given oxygen and placed in Fowler's position. Venous pressure was 9 cm. of water. An abdominal paracentesis yielded 15 liters of clear straw-colored fluid with a specific gravity of 1.016, containing 1,000 cells (no differential cell count reported). Examination following this revealed no palpable masses in the abdomen. The patient was more comfortable. Basal metabolic rates of —50%, —31%, and —43% were obtained, and less than 1 μc of I^{131} was taken up after ingestion of 50 μc. Edema of the extremities decreased, but ascitic fluid reaccumulated.

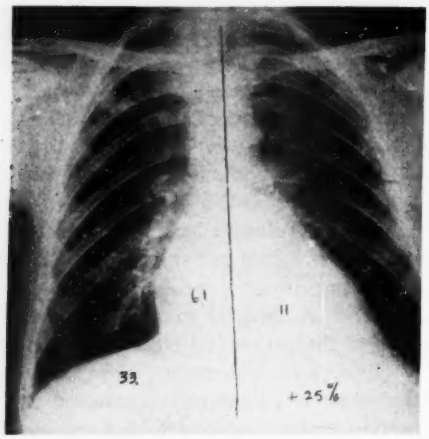

Fig. 1.—X-ray showing initial cardiac enlargement.

On the 14th hospital day ¼ grain (15 mg.) of desiccated thyroid twice weekly was ordered, followed after an interval by some subjective improvement, and on the 25th hospital day the dose was increased to ¼ grain (15 mg.) of thyroid daily. At this time the patient weighed 224 lb. (100.8 kg.). On the 32nd day the dose was increased to ½ grain (30 mg.) daily. However, by the 39th day his weight had increased 8 lb. (3.6 kg.) and, because of increasing ascites, a second paracentesis was done, yielding 12 liters of amber fluid with a protein content of 4.0 gm. per 100 cc. (albumin 2.5 gm. and globulin 1.5 gm. per 100 cc.). This fluid contained 50 cells per cubic millimeter. The patient's weight after paracentesis was 207 lb. (93.2 kg.).

On the 47th hospital day there developed over the precordium a loud adventitious sound suspected of being pericardial in origin but not typical of a pericardial friction rub. It disappeared three days later, only to reappear after a three-day interval. By this time the thyroid had been increased to ¾ grain (45 mg.) daily. The patient's subjective improvement was so favorable that we had difficulty in restricting his activity. On the 51st hospital day, one day prior to the recurrence of the murmur, the patient's weight had increased 3 lb. (1.4 kg.) and he complained of shortness of breath. On the 52nd day a loud systolic murmur was again heard. This was confirmed by a phonocardiogram. The dyspnea increased, and orthopnea was noted as well as tachycardia. Venous pressure was 6 cm. of water. On the 53rd day, thyroid was discontinued and meralluride sodium (Mercuhydrin) and digitoxin were used for the first

time, with a resultant loss of weight and relief of dyspnea. The patient improved. The murmur disappeared suddenly after being present three days, and after another three-day interval (59th day) thyroid medication was resumed in a smaller dose, ¼ grain (15 mg.) daily. Uninterrupted improvement followed, and the dosage of thyroid was increased. At the time of discharge, Aug. 27, 1952 (131st day), the patient was receiving 1¾ grains (105 mg.) daily. Examination showed a blood pressure of 120/80. The heart was normal in size (Fig. 3; chest x-ray Sept. 29, 1952), there were no murmurs, the lung fields were clear both by physical examination and x-ray, the abdomen contained no ascites (Fig. 4) or palpable masses, extremities were without edema, the skin was of normal texture, the patient was alert, pubic and axillary hair was present, and libido had returned.

On Sept. 29, on return for follow-up study, the patient's basal metabolic rate was —2%. He was cheerful, working some about his home, and asymptomatic except for slight anginal pain on effort. The thyroid dosage was reduced, and the patient was advised to keep his

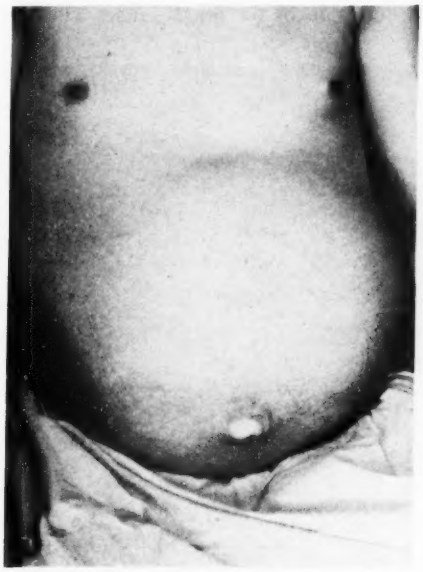

Fig. 2.—Photograph showing abdomen distended with ascites. The umbilical hernia is noted.

activity below the level that would cause anginal pain. On Oct. 21, 1952, he died suddenly at home after modest exertion preceded by severe chest pain. There was no autopsy.

Results of the following laboratory studies were within normal limits: nonprotein nitrogen, serum sodium, serum potassium, blood glucose, urinalysis, leucocyte count, serum cholesterol, cephalin flocculations, and plasma proteins. The erythrocyte counts varied from 3,700,000 to 4,200,000 per cubic millimeter. Thymol turbidity tests were 3 and 5 units on two determinations. A sulfobromophthalein (Bromsulphalein) test showed 7% retention of dye in 45 minutes. Alkaline phosphatase was 8.0 units. Basal metabolic rates initially were —50%, —31%, and —43%. At the time of discharge it was —13%. I^{131} study showed an uptake of less than 1 μc by the thyroid gland with an oral dose of 50 μc, and the protein-bound iodine was 0.006 μc. This was interpreted as being compatible with myxedema.

Review of Case 1 (H. F.).—A review of this patient's service record reveals that he had had a basal metabolism test during hospitalization prior to discharge from the Army. This was normal and had been done because of the presence of a total alopecia, which he had had since the age of 17. Hypothyroidism seemed

present soon after 1946 according to the history, and myxedema gradually developed during the ensuing six years. He was recognized as having myxedema on admission to this hospital. Laboratory confirmation of the disease was completed prior to specific therapy. Abdominal paracenteses were done because of the severity of the ascites and its effects on respiration. Normal venous pressures were recorded. Response to thyroid was excellent. This was started in a dosage we considered conservative, ¼ grain (15 mg.) twice weekly. The subjective improvement, we believe, led to physical activity difficult to control, and this in turn plus the increasing dosage of thyroid led to the symptoms suggestive of left ventricular failure. This type of eventuality is referred to by McGavack.[3] It led to discontinuation of thyroid therapy temporarily and the treatment of the symptoms of heart failure. The murmur which developed was probably due to a mitral insufficiency as a result of dilatation of the mitral ring. The association of coronary

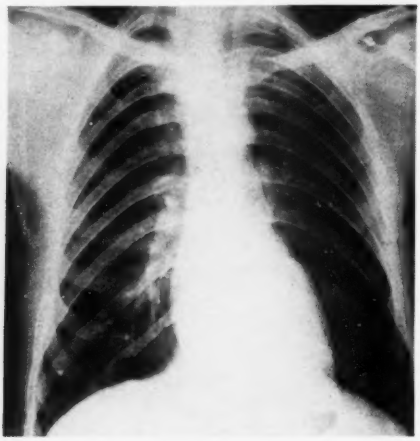

Fig. 3.—X-ray showing normal heart size following therapy.

artery disease in a patient with myxedema and disturbed cholesterol metabolism is justifiably suspected.[3] Whether insistence on rehospitalization for a prolonged period when angina pectoris of effort was recognized and more drastic reduction of the thyroid dosage would have materially affected this patient's course is problematical.

Case 2.—J. E. McK., a 64-year-old white man, transferred to the Veterans Administration Hospital, Hines, Ill., from a Veterans Domiciliary Center, on Dec. 19, 1950, complained of swelling and discomfort of the abdomen. He had noticed some shortness of breath on exertion but he gave no history of orthopnea, nocturnal dyspnea, or swelling of the legs. Until the age of 49 he had worked steadily as a plumber and steam fitter but since then had not worked regularly, spending most of his time in hospitals or domiciliary homes. His past history also revealed a habit of drinking about two "shots" of whiskey and two bottles of beer daily for many years. He had noted slight rectal bleeding, particularly when constipated. He had no food intolerance and no history of jaundice or indigestion or significant change of weight.

On admission he weighed 164 lb. (73.8 kg.), his pulse rate was 70, and his blood pressure was 140/80. He was described as haggard and pale, appearing chronically ill. His skin was dry and wrinkled and he spoke with a low husky voice, but he was oriented and cooperative. The thyroid gland was not palpable. The cervical veins were not distended. The lungs were normal

on percussion and auscultation. The abdomen was moderately distended; a fluid wave was elicited, and shifting dullness was noted. An abdominal wall hernia was present just above the umbilicus. The liver and spleen were not palpable. The extremities were free of edema. There were no spider nevi. The skin was pale and dry. The urine was normal, erythrocyte count 4,100,000, and the nonprotein nitrogen 29 mg. per 100 cc. The plasma protein was 7.0 gm. (no albumin-globulin ratio reported). Cholesterol was 340 mg. per 100 cc., thymol turbidity 1 unit, and the cephalin flocculation test was negative. The basal metabolic rate was —21%. I^{131} with a tracer dose of 50 μc showed less than 1 μc uptake. Protein-bound iodine was 0.029 μc per liter. These tests were interpreted as compatible with hypothyroidism. The electrocardiogram was reported as probably normal. Chest x-ray revealed a 16% cardiac enlargement. Stools contained no occult blood. Gastrointestinal x-rays were normal.

This patient was started on desiccated thyroid, ½ grain (30 mg.) doses daily; this was increased weekly until he was taking 2 grains (120 mg.) per day. In addition, he received a high-

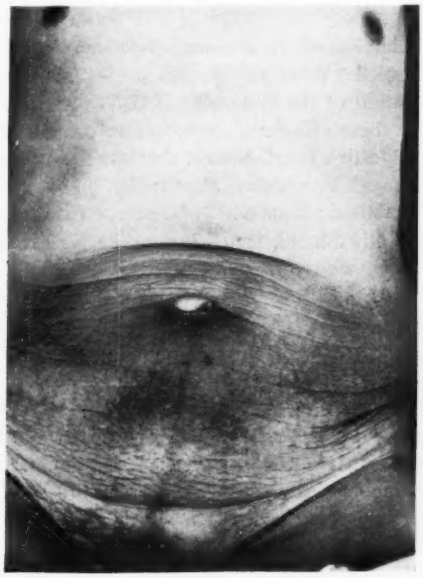

Fig. 4.—Photograph showing abdomen after treatment had controlled accumulation of ascitic fluid.

protein diet with vitamin supplements. Because of the alcoholic history, cirrhosis of the liver as a cause of the ascites was considered initially. He was given two injections of 1 cc. of mercaptomerin sodium (Thiomerin) early in his hospital course and afterwards was given no further diuretics. He lost 19 lb. (8.5 kg.) in three months. In addition, he became more alert and took increased interest in his surroundings. When discharged, he had no ascites. X-ray of the chest showed a normal cardiac size.

Review of Case 2 (J. E. McK.).—This case, we believe, illustrates classically the slowly progressive development of myxedema, possibly over a period of 15 years on the basis of the history. The picture is one of a person profitably and regularly employed until about the age of 49, after which he apparently became unable to work and spent time in hospitals and domiciliary homes. His ascites was not massive, and no paracenteses were necessary. The general physical and mental response of the patient to thyroid therapy was gratifying, but the response

of the ascites to thyroid medication was obscured partially by the use of the two injections of mercaptomerin sodium early in his hospitalization. This therapy, in retrospect, now seems unnecessary, serving only to hasten the mobilization and excretion of this effusion.

COMMENT

The older literature contains sporadic reports of ascites occurring in myxedema.* In recent years a controversy has arisen as to whether the ascites is due to congestive heart failure. Rundle [7] indicates that in myxedema protein-rich effusions occur in the pleural and peritoneal cavities in addition to the pericardial cavity, even in the absence of congestive failure. Watson [2] states that the presence of mucin in the fluid in myxedema indicates that ascites is directly related to the underlying cellular disturbance of the disease, i. e., elaboration of an abnormal fluid rich in mucin.

Obviously the mechanism or mechanisms involved in the formation of these effusions is not understood. Whether the presence of effusions is an index of the severity or of the duration of the disease or both has apparently not been stated. It seems certain, since these effusions are richer in protein than is the fluid seen in these cavities in congestive heart failure, that the fluid in myxedema is "metabolic" in etiology. Lange [8] believes an abnormally high capillary permeability to be the cause of the "interstitial edema and polyserous effusions."

McGavack,[3] on the other hand, states that ascites is rarely a part of the clinical picture of myxedema. Fahr,[5] in 1928, reported a series of cases of myxedema with polyserous effusions, which he believed were due to congestive heart failure (myxedema heart disease).

While the clinical picture in patients with myxedema may be quite suggestive of congestive heart failure, there do exist differences of very fundamental nature which tend to throw doubt on the situation being identical with conventional heart failure. The data in Case 1 demonstrate some of these points: The venous pressure was found to be normal, and marked edema and ascites were present. Ascitic fluid showed a much higher protein content than is present in congestive failure. The marked decrease in cardiac size to normal on thyroid therapy is contrary to experience in the common types of heart disease.

Other investigators have recorded important data in myxedematous patients not characteristic of heart disease. Ellis and co-workers,[9] in cardiac catheterization studies on myxedematous patients not having other organic heart disease, found that for the most part the physiological findings were consistent with a low cardiac output which paralleled the decreased oxygen consumption. Others have found the cardiac output to be decreased to somewhat greater extent than oxygen consumption. However, Stewart and co-workers [10] believe that this is a different situation from that noted in conventional heart failure and that it is primarily due to the slowing of the circulation. In spite of the cardiac size being increased and the electrocardiogram being abnormal, Ellis found there was no increase in the right heart or pulmonary artery pressures. Even in one case in which he demonstrated dyspnea and edema clinically he found no alterations in pressure. Venous pressure has usually been found to be normal. Circulation time may be normal but is commonly lengthened, consistent with the low cardiac output. Blood vol-

* References 5 and 6.

umes have been found to be consistently reduced rather than increased. These findings have made it difficult to define the status of the heart in myxedema. The definite enlargement of the heart by x-ray and the abnormality of the electrocardiograms noted in this disease are the most important factors pointing to a myxedema heart disease.

The striking changes in the electrocardiogram toward normal which frequently follow the administration of thyroid medication are also not consistent with the usual observations in organic disease of the heart. Such changes are compatible with the reversal seen in known physiological disturbances of other types when corrected. Even though the exact reason for these abnormalities is unknown, it seems that an anatomical basis is unlikely. When improvement does not occur after adequate thyroid medication in myxedema, it is probable that a basic organic disease of the heart per se is present. The proper explanation of the cardiac enlargement in myxedema has long been a subject for discussion. Pericardial effusions have been demonstrated by Feasby,[11] Lerman and co-workers,[12] and Kern, Soloff, Snape, and Bello.[4] Pericardial effusion has also been demonstrated in experimental hypothyroidism by Goldberg [13] and Tatum.[14]

Kern and co-workers [4] added evidence which suggests that pericardial effusion is a constant and early occurrence in myxedema. It is obvious that pericardial effusion would well explain the cardiac enlargement and the remarkable decrease in size under therapy. This explanation is not universally accepted by all writers as being adequate. McGavack [3] refers to pericardial effusion as occurring in some cases of myxedema but believes cardiac enlargement is not always due to this cause. Other investigators have suggested that the increase in size of the heart might be accounted for by the generalized nutritional disturbance being reflected in the myocardium as interstitial edema similar to that found in other tissues. Lerman, Clark, and Means [12] observed that there may appear to be edema of the muscle fibers. Increased water content of the myocardium has been demonstrated in thyroidectomized animals. LaDue [15] described nonspecific changes in the myocardium but did not find any evidence of organic changes specific for myxedema.

From the physiological data available, it does not seem that there is any reason for dilatation of the heart to compensate for an inefficient output. Friedberg [16] concludes that there is no convincing evidence that cardiac hypertrophy occurs as a direct result of myxedema. At the present time one may conclude that the only factor responsible for cardiac enlargement directly due to myxedema is pericardial effusion. However, it should be kept in mind that there is a relatively high incidence of coronary artery disease and also hypertension among these patients which might cause hypertrophy and/or dilatation.

Ellis and co-workers [9] suggest that pulmonary edema may occur in this disease as the result of alterations of body protein. This, associated with the disturbed capillary permeability, may well be responsible for the edema of body tissues in the absence of conventional congestive heart failure. It is improbable that there exists a specific myxedema heart disease, but rather the manifestations are those of generalized metabolic disturbances affecting all tissues of the body, including the heart.

Though it is difficult by ordinary clinical examination to differentiate between the manifestations of myxedema and those due to primary cardiac failure, it seems that in Case 1 left ventricular failure did develop in the course of thyroid medication.

Initially this patient conformed to the usual clinical concept of myxedema, but after having shown an excellent response to thyroid medication, with dissipation of excess body fluid and a marked increase in physical activity, he developed rather acute dyspnea, orthopnea, and signs of pulmonary congestion. That this was left ventricular failure is further confirmed by evidence of cardiac dilatation (transient mitral systolic murmur) and the prompt response to digitalis and mercurial diuretics. The final episode of sudden death, which was preceded by precordial pain, suggests that coronary arteriosclerosis was probably of fundamental importance as a causative factor of the left ventricular failure. Also, the fact that the electrocardiogram did not show the expected return to normal suggests the presence of advanced coronary artery disease.

Such an incident of acute myocardial failure serves to emphasize the caution necessary in the supervision of physical activity during the treatment of myxedema. The increased metabolic demands place increased work on the heart. This with the increased physical activity associated with improved sense of well-being and ambition of the patient may well exceed the capacity of the heart, even though it is otherwise normal. This is particularly true if the myxedema has been advanced and of long standing. Here, in addition to the myocardium having been subjected to general metabolic derangement, the heart has become adapted to a state of low physiological demand (deconditioned) and considerable time spent in slowly graduated activity is indicated. If there exists also a basic organic disease, this matter assumes even greater importance. It would seem that true congestive heart failure is most likely to occur in the stage of recovery from myxedema. It is possible that if the activity in Case 1 had been supervised closely for a long period of time death might not have occurred. For these reasons a patient should never be "exploded" out of a myxedematous state. The warnings often repeated in the literature in this regard are of sound physiological reasoning.

From the foregoing, it is believed that ascites is an aspect of the metabolic disease and should not be considered a manifestation of conventional heart failure. It is also tempting to speculate, despite confusion and differences of opinion as to the frequency of serous effusions, as to whether ascites is not also a constant and major finding in myxedema—consistent with Kern's conclusion that pericardial effusion is a constant, major, and early finding in myxedema. Electrocardiographic findings and x-ray for a long time suggested abnormalities of the heart or its sac. We cannot study the peritoneal cavity in a similar manner. The thought of abdominal paracenteses to attempt to prove the presence of a minimal ascites is not a tempting one, since ordinarily abdominal taps are done only for very justifiable reasons. While it must be stated that a study of the limited number of cases of myxedema which were autopsied does not support the theory that ascites is common in myxedema, it must be pointed out that autopsy reports † are relatively few in number compared with the total number of myxedema cases known to occur. It must also be pointed out that these autopsies may not be done at a time in the course of disease appropriate to demonstrate ascites.

† References 12, 15, and 17-19.

SUMMARY

Two cases of myxedema with ascites are presented, one case with an ascites sufficient to justify multiple abdominal paracenteses.

The rarity of clinically determinable ascites in patients with myxedema is pointed out.

The question is raised as to whether ascites is a part of the myxedema picture as is pericardial effusion, according to the investigations of Kern and co-workers.[4]

The difficulty in differentiating ascites due to myxedema per se from ascites associated with anasarca due to conventional congestive heart failure is discussed.

This report emphasizes the need for caution in the dosage of thyroid and discusses the complications that may occur even with moderate doses of the drug.

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Case Reports

TREATMENT OF SYSTEMIC BLASTOMYCOSIS WITH 2-HYDROXYSTILBAMIDINE

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BROOKLYN

PRIOR to the introduction of stilbamidine in the treatment of systemic blastomycotic infections, by Schoenbach and co-workers,* there had been no generally effective therapy for this disease, although administration of iodides in conjunction with desensitization has been reported to have been successfully used in the treatment of some cases.[3] Elson's observation that certain diamidines exerted a fungistatic effect upon Blastomyces dermatitidis [4] led to the clinical trial of stilbamidine in patients who had systemic blastomycotic infections. The therapeutic results obtained in the treatment of this disease were excellent.† Subsequently, Snapper and co-workers treated patients with extensive blastomycotic infections with 2-hydroxystilbamidine with good results. ‡

Stilbamidine is one of the aromatic diamidines which has been used effectively in the treatment of kala-azar. However, because of undesirable sequelae developing in patients treated with this drug, it has been replaced to a great extent by propamidine, a less effective agent in the treatment of kala-azar, but one causing fewer undesirable reactions.[6] The immediate toxic effects of stilbamidine may include a fall in blood pressure, generalized formication, sweating, breathlessness, dizziness, nausea, epigastric discomfort, and vomiting. The slow intravenous administration of stilbamidine solution has been reported to prevent these immediate undesirable effects.[6] In addition to these immediate effects, a unique dissociated neuropathy, usually confined to the trigeminal nerve area of distribution, has been observed to appear two to five months after treatment with stilbamidine.§ The sensory changes observed have been progressive paresthesias and anesthesia to light touch but with preservation of the sense of pressure and pain over the affected area. The mechanism of this neuropathy is obscure but may be due to toxic products produced when stilbamidine is exposed to sunlight.[11] The symptoms produced may disappear over a period of several months, but in some patients they have remained indefinitely. It is obvious that a drug which would be as effective as stilbamidine in the treatment of systemic blastomycosis but yet which would not cause the undesirable effects of stilbamidine would be desirable in the treatment of this disease.

Dr. R. C. Pogge, of The Wm. S. Merrell Company, generously supplied the 2-hydroxystilbamidine used in this study.

From the Medical Services of the Maimonides Hospital and the Department of Medicine, State University of New York College of Medicine at New York City.

* References 1 and 2.

† References 1 and 2.

‡ References 5 and 12.

§ References 2, 6, and 7.

2-Hydroxystilbamidine has been reported to be as effective against leishmaniasis, bacteria, and fungi as stilbamidine.[4] This compound has been used in the treatment of multiple myeloma,[9] visceral kala-azar,[10] and mucocutaneous leishmaniasis [11] without the development of troublesome neurologic sequelae. It has been used in the treatment of systemic blastomycosis, with favorable clinical response.‖

It is the purpose of this paper to report a case of systemic blastomycosis treated with 2-hydroxystilbamidine, with an excellent response to treatment. Although this patient was given a large total dose of 2-hydroxystilbamidine, he has not developed the delayed neuropathy which is noted even after much smaller doses of stilbamidine.

REPORT OF A CASE

A 22-year-old Air Force enlisted white man, on active duty in England, became ill about May 1, 1952, with a complaint of right-upper-quadrant pain. X-ray examination of the chest on May 15, 1952, revealed a segmental collapse of the lower posterior portion of the right upper lobe. This was thought to be due to a viral pneumonia, and the patient was treated with antibiotics, without improvement. Increasing fatigue, a cough productive of rust-colored sputum, and low-grade fever appeared. Repeat x-ray examination of the chest revealed increasing infiltration of the right upper lobe. Leucocytosis and an elevated sedimentation rate were present. Further treatment with penicillin and chlortetracycline (Aureomycin) was given, with no improvement in the patient's condition. Repeated smears for tubercule bacilli were negative.

The patient was transferred to another army hospital in England for further study. Admission physical examination revealed a small area of dullness to percussion and bronchial breath sounds along the medial aspect of the right scapula. The physical examination revealed no other abnormalities.

Numerous sputum samples and gastric washings were examined and cultured for tubercle bacilli, but none were found. A first-strength tuberculin (purified protein derivative; PPD) test was negative, but a second-strength PPD test was positive. On bronchoscopic examination no abnormalities were found, and tissue taken from the right upper lobe bronchus was reported as "non-specific granulation tissue."

The patient developed severe pain in his neck. A spinal tap at this time revealed normal dynamics, no cells, and a protein content of the fluid of 24 mg. per 100 cc. The patient developed some weakness of the left deltoid muscles. "Walnut sized" nodules appeared in the right vastus lateralis muscle and over the right Achilles tendon, and some edema of the right ankle appeared.

On July 23, the patient was found to have developed a complete flaccid paralysis of the left shoulder girdle muscles. Repeat spinal fluid examination revealed normal dynamics, no cells, and protein of 84 mg. per 100 cc. The paralysis cleared almost completely in about six weeks.

Biopsy of the nodule in the right vastus lateralis muscle revealed a grossly caseous mass. Microscopic examination revealed poorly vascularized granulation tissue, including numerous collections of epithelioid cells surrounded by chronic inflammatory reaction, and central caseation, which was considered typical of tuberculosis.

The patient was transferred to the United States with a diagnosis of disseminated tuberculosis.

Physical examination on admission to the hospital, Sept. 28, 1952, revealed a chronically ill young man. Positive physical findings noted were a small vesicle at the right nasolabial fold, a nodular lesion on the hard palate, a nontender 2 cm. nodule on the right Achilles tendon, a warm swollen area distal to the left lateral malleolus, and minimal nuchal rigidity. X-ray examination of the chest revealed an infiltration of the right upper lobe of the lung.

‖ References 5 and 12.

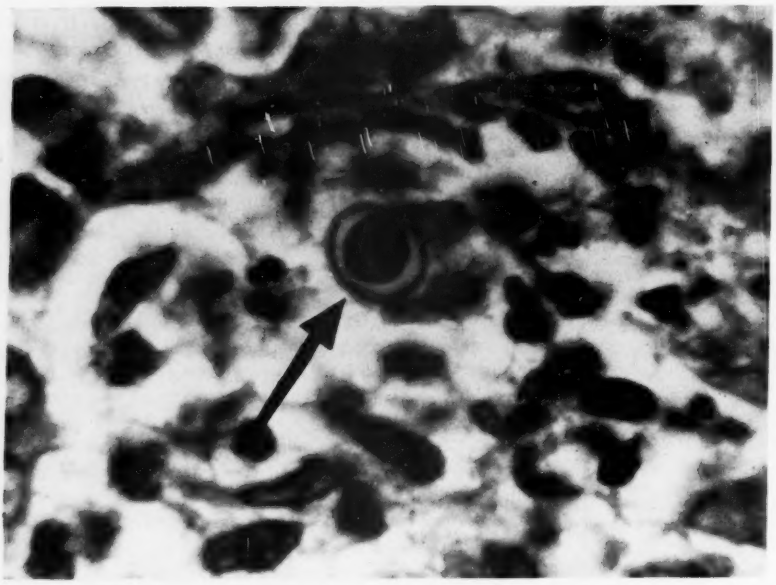

Fig. 1.—Blastomyces dermatitidis in tissue from nose of patient; × 980.

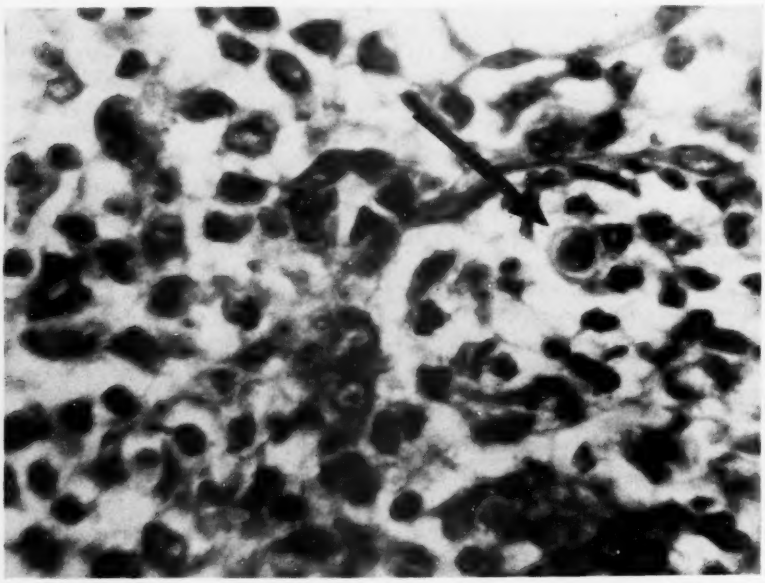

Fig. 2.—Blastomyces dermatitidis in tissue from nose of patient; × 440.

On Oct. 13, 1952, biopsy of the nodule on the right Achilles tendon was performed. Microscopic examination of this tissue revealed "a chronic granulomatous tendonitis with central caseation, giant cells, and one thin-walled spherical body within a giant cell." This suggested a blastomycotic infectious process. Other granulomatous nodules appeared over the left wrist and right nasolabial fold. Biopsy of the nasolabial nodule was performed on Jan. 15, 1953, and on April 8, 1953. The biopsy of April, 1953, revealed a "severe granulomatous process of the skin showing marked pseudoepitheliomatous hyperplasia with scattered microabscesses, in the center of which are doubly refractile spherules with large blue nuclei and occasional definite budding." This was considered characteristic of blastomycotic infection. In addition, on culture of the tissue from this biopsy there was growth of typical B. dermatitidis organisms. The patient developed increasing neck pain, and x-ray examination of the cervical spine revealed involvement of the fourth to seventh cervical vertebral bodies by a destructive process. Examination of the spinal fluid revealed 18 WBC per cubic millimeter, with a differential count of 7 polymorphonuclear leucocytes and 12 lymphocytes.

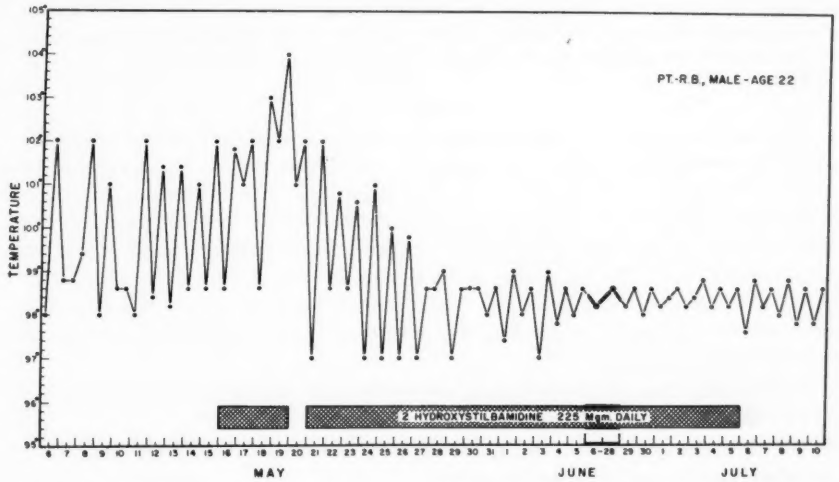

Fig. 3.—Temperature response of patient with disseminated blastomycosis treated with 2-hydroxystilbamidine.

During the course of the illness, the patient's temperature had remained around 99 F. until April 17, 1953, at which time there was a progressive rise, until it reached levels of 102 F. daily (Fig. 3).

On May 15, 1953, treatment with hydroxystilbamidine was begun.

Physical examination at this time revealed a chronically ill young man with granulomatous lesions of the right nasolabial fold and left middle finger. There was a nodule 3 by 3 cm. in the left cervical region. Another mass protruded from the hard palate. The patient held his neck almost immobile because of pain on motion. Chest examination revealed some impairment of breath sounds over the right upper lobe. Abdominal examination revealed the spleen to be 3 fingerbreadths below the costal margin.

Beginning on May 16, 1953, 2-hydroxystilbamidine, 225 mg. dissolved in 250 cc. of 5% dextrose solution, was administered intravenously daily for a period of 50 days. The drug was dissolved in the dextrose solution immediately before it was to be administered. It was then given in a slow drip over 45 minutes to 1 hour. The patient received the drug without reaction, except on the third and fourth days of treatment, when the temperature rose to 103 and 104 F., respectively. This increase in temperature was thought to be due to a modified Herxheimer reaction, such as has been reported after diamidine therapy of kala-azar.[6]

The patient's temperature then fell progressively until it reached normal levels, on the 15th day of treatment. An initial weight loss of 6 lb. (2.7 kg.) occurred, but as therapy was continued this weight was regained. Besides the return of temperature to normal, regression of all granulomatous lesions was noted. The neck pain was so markedly decreased that the patient could move his neck freely. The spleen became nonpalpable. A total dose of 11.25 gm. of 2-hydroxystilbamidine was administered to the patient over a 50-day period. The patient was sent home on a 30-day leave, during which time he remained apparently well and, in addition, continued to gain weight until he weighed his normal weight, of 130 lb. (58.5 kg.). X-ray examination of the cervical spine revealed healing of the destructive osseous lesions. Chest x-ray showed complete clearing of the infiltrative process in the lung.

As a result of healing of the lesion on the nose, scarring and narrowing of the right nostril occurred, which necessitated plastic repair. Microscopic examination of the tissue, removed at this time, revealed only chronic granulation tissue, whereas prior to therapy numerous organisms had been noted in biopsy material from this area.

Hematological studies and hepatic and renal function tests revealed no evidence of toxicity to these organs during the course of 2-hydroxystilbamidine therapy. Signs and symptoms of a dissociated trigeminal neuropathy, which frequently occurs following administration of stilbamidine, has not appeared in this patient treated with 2-hydroxystilbamidine.

COMMENT

A patient with systemic infection with Blastomyces dermatitidis was treated with 2-hydroxystilbamidine. There was regression of pulmonary, osseous, and cutaneous lesions. The patient became afebrile 15 days after institution of therapy. A Herxheimer reaction developed on the fourth and fifth days of treatment but did not necessitate cessation of therapy. The total dose used in this patient was 11.25 gm., given intravenously over a 50-day period at the rate of 225 mg. daily dissolved in 250 cc. of 5% dextrose solution. The exact dosage needed for treatment of this disease is unknown, but treatment in this case was continued until evidence of healing in all involved areas appeared.

Stilbamidine has been reported to cause the toxic neurological sequelae noted above after as little as 2 gm. have been administered.

To date, dissociated neuropathy, which has been observed after the use of stilbamidine, has not appeared in this patient.

2-Hydroxystilbamidine should be made up in solution just prior to administration and should be administered by slow intravenous drip over a period of 45 minutes to 1 hour. If the drug is made up in solution and allowed to stand before being administered to the patient, nausea and vomiting may occur.¶

¶ Colsky, J.: unpublished data.

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News and Comment

ANNOUNCEMENTS

New Institute of Microbiology.—The anniversary of the discovery of streptomycin in an obscure and crowded Rutgers University laboratory a little more than 10 years ago will be marked at New Brunswick on June 7 with the dedication of the new $3,500,000 Institute of Microbiology—a building made possible by the life-saving drug and dedicated to research.

The new Institute is a handsome addition to the State University's science campus across the Raritan River.

The formal dedication, on June 7, will be followed by a two-day scientific symposium on June 8 and 9. More than 400 scientists from this country and abroad have been invited to the session, which will have as its theme, "Perspectives and Horizons in Microbiology."

Dedication of the Institute will mark another step in the strengthening and broadening of research in microbiology which was started at Rutgers in 1914, when Dr. Selman A. Waksman, first director of the Institute, began his studies of actinomycetes. That research 25 years later led Dr. Waksman to launch a study of the production of antibiotics by acinomycetes and eventually to streptomycin, for which he was awarded the Nobel Prize in Medicine and Physiology in 1952.

The discovery of streptomycin was the result of a program of systematic research that first produced actinomycin and streptothricin, which proved too toxic in animal experimentation. Then, on Aug. 20, 1943, continuing study of the actinomycetes produced streptomycin, first isolated from a strain of the microbe from the swab from a chicken's throat.

No announcement of streptomycin was made until January, 1944. In April, streptomycin's activity against Mycobacterium tuberculosis was demonstrated. Its ability to control various Gram-bacteria disease in animals was announced four months later. In November, Dr. Waksman gave the first public address before the Mayo Foundation and Clinic on the subject of the potentialities of streptothricin and streptomycin in the control of infectious disease.

December, 1944, produced another important milestone. That month, Dr. W. H. Feldman and Dr. H. C. Hinshaw, of the Mayo Clinic, established experimentally that streptomycin was more effective against tuberculosis than any previous drug.

Two years later, first reports of the treatment of large numbers of clinical cases recommended that streptomycin be used in the treatment of pulmonary tuberculosis and various other forms of the disease. The most spectacular results, however, were obtained in the use of streptomycin against miliary tuberculosis; tuberculous meningitis; laryngeal, bone, and joint tuberculosis, and various other special forms of the disease.

It is now used successfully with paraaminosalicylic acid (PAS) and with various forms of isonicotinic acid hydrazide (INH). The supplementary use of these compounds has reduced the toxicity of streptomycin and retarded the development of resistance to the drug by the tuberculosis organism.

Although streptomycin is primarily used in the treatment of tuberculous diseases, large quantities are also being used against other infectious diseases of man, and it has found many other applications, such as the preservation of virus vaccines and the semen of animals, in the treatment of certain plant diseases, and to some extent in animal feeding. It is also used in the treatment of certain infectious diseases of animals.

Streptomycin production has created a great new industry. Production in one year has nearly reached the $100,000,000 mark. In the United States alone last year nine companies

produced between 15,000,000 and 20,000,000 gm. a month. It is also manufactured in two plants in Great Britain; two in Spain; one each in Sweden, Denmark, and Germany; three each in France and Italy; four in Japan, and probably several in countries behind the Iron Curtain.

Royalties from the manufacture of streptomycin have amounted to more than $4,000,000, of which more than 80% have been assigned to the Rutgers Research and Endowment Foundation. It is from these funds that the new building has been constructed and equipped.

The ARCHIVES, along with thousands of other well wishers, salutes Dr. Waksman and Rutgers University School of Medicine on the brilliant achievements of the past 11 years.

Research Fellowships in Public Health Mental Health.—The National Institutes of Health, Bethesda, Md., is announcing new research fellowships in the area of "public health mental health." The program is designed to assist young scientists and physicians in obtaining training and experience in research techniques which may be applied to the problems of mental health and illness.

Research fellowships are available to qualified research workers in many different fields of science and medicine. A booklet describing these traineeships has just been issued and may be obtained by addressing the National Institute of Mental Health, Bethesda 14, Md.

Second Congress of the International Diabetes Federation.—The Second Congress of the International Diabetes Federation will be held in Cambridge, England, July 4-8, 1955. Sir Lionel Whitby, K.V.O., M.D., Master of Downing College, Cambridge, will be honorary president.

The London Diabetic Association will act as host. Future publications in connection with the Congress will be issued by Mr. James G. L. Jackson, Acting Secretary General of the Association.

Books

Year Book of Endocrinology, 1952. Edited by Gilbert S. Gordan, M.D. Price, $5.50. Pp. 400, with 107 illustrations. Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1953.

The various volumes of the Year Book series have won well-deserved popularity, and this one is no exception. The field is comprehensively covered and the abstracts, or rather condensations, are not too brief. Critical comments by the editors further enhance the value and usefulness of the book. There are numerous illustrations and an index.

Physiologic Effects of Wounds. By the Board for the Study of the Severely Wounded, North African-Mediterranean Theater of Operations. Price, $3.50. Pp. 376. Office of the Surgeon General, Dept. of the Army, Washington, D. C., 1952.

In 1944, the Commanding General, North African Theater of Operations, appointed a medical board to study the treatment of the severely wounded. This group, with the late Tracy B. Mallory as its chairman, included H. K. Beecher, C. H. Burnett, S. L. Shapino, F. A. Simeone, L. D. Smith, and E. R. Sullivan and their report was edited by Dr. Beecher. The problems of performing multiple chemical tests on blood and urine of recently wounded men under army field conditions in Italy must have been immense. As a result of these efforts there is assembled in this book a mountainous collection of data from 186 wounded men regarding so-called lower nephron nephrosis, shock, liver function, and the crush syndrome, with particular emphasis on the first-named. Data are presented completely in tabular and often in graphic form, with some discussion. The chief value of the volume in its present form will be as a source of data on physiologic and pathologic changes in the severely injured human being to be used by the investigator rather than as a guide for the practitioner.

Chronic Iliac Pain in Women. By H. B. Atlee, M.D. Price, $2.50. Pp. 65, with 6 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1954.

The controversial subject of chronic iliac pain in women is handled in a very skillful and logical manner. This easy-to-read discussion involves a medical syndrome that has been ignored, overemphasized, and incorrectly used as a surgical indication as much or more than any other in female surgery. Here is an enlightening debunker for all doctors who see women as patients, and for the most part it will have the hearty approval of all teaching gynecologists.

The Physician in Atomic Defense. By Thad P. Sears, M.D. Price, $6.00. Pp. 308, with 53 illustrations. Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1953.

As Dr. Waring says in his thoughtful foreword, whether we like or not the "atomic age" is here and atomic energy will no doubt be used for peaceful purposes as well as for war. Injuries are therefore bound to occur even in civilian life, and it behooves doctors to know what to do to fend off the disastrous effects of atomic agents. Dr. Sears has done a fine job of clearly presenting in not too technical language every facet of the subject; certainly everyone seriously interested in industrial practice or civilian defense needs to study carefully and have at hand a manual of this sort, even if at times it makes dreary reading. The book is handy and well printed, and there are many diagrams and photos. Many references to the literature are cited.

Multiple Myeloma. By I. Snapper, M.D.; Louis B. Turner, M.D., and Howard L. Moscowitz, M.D. Price, $6.50. Pp. 168. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1953.

No one is better qualified than Dr. Snapper and his associates to write about multiple myeloma. Dr. Snapper has been interested in the subject for years, not only in connection with the myeloma cell but also in connection with bone disease in general. He also was the man who introduced stilbamidine in the treatment of myelomatosis. After an interesting historical

introduction there is a chapter on the myeloma cell, and following this the subject is taken up systematically dealing with symptoms, metabolic abnormalities, pathology, differential diagnosis, and treatment. It is disappointing of course that nothing very effective is offered by Dr. Snapper. He speaks of x-ray treatment, of stilbamidine, and of urethane. None of these agents, as everyone knows, is highly effective, and multiple myeloma remains essentially an intractable and hopeless disease. Formulation of the whole subject, however, in simple and attractive format of this sort, is certainly useful.

Cold Injury: Transactions of the Second Conference, Nov. 20 and 21, 1952. By M. Irene Ferrer, M.D., Editor. Price, $4.00. Pp. 242, with 42 illustrations. Josiah Macy, Jr., Foundation, 16 W. 46th St., New York 36, 1953.

Although cold injury has always been a problem of war, greater progress has been made in an understanding of this condition since the recent Korean conflict. This kindling of interest has led to rather extensive studies in its epidemiology, pathophysiology, prevention, and treatment.

Although there are some intersting discussions in these transactions of the second conference on cold injury, yet this volume is mainly for the experts who are particularly interested in this subject. For this group it is an excellent reference of new material, new thoughts, and plans for future research.

Diabetic Care in Pictures. By Joseph Rosenthal, M.D., and Helen Rosenthal, B.S. Price, $3.00. Pp. 164, with 128 illustrations. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5; Aldine House, 10-13 Bedford St., London, W.C. 2; 2083 Guy St., Montreal, 1953.

The information in this book is stated simply and should be easily understood by the average lay person. It concerns normal and diabetic diets, insulin, insulin reactions, acidosis, diabetic coma, tests of blood and urine, cutaneous injuries, infections, and hygiene. A short discussion about personal and social factors is included.

The sketches of food exchanges have no quantitative aspects; they are based on those developed by the American Diabetes Association, which are approved by most physicians and dietitians.

The pictures showing the methods used in urinalysis and insulin technique are good. The method of sterilizing the syringe and needle used for injection of insulin is not universally accepted; many physicians prefer to have the syringe stored in alcohol, but evidently the authors have not encountered any difficulties with the technique they describe. All in all, this is a most satisfactory book for the instruction of the diabetic patient.

Administrative Medicine: Transactions of the First Conference March 9-11, 1953. Edited by George S. Stevenson, M.D. Price, $3.00. Pp. 176, with 6 illustrations. Josiah Macy, Jr., Foundation, 16 W. 46th St., New York 36, 1953.

The rather ambiguous title of "Administrative Medicine," which is a transcript of a Josiah Macy, Jr., Foundation Conference, suggests high-flown thoughts on how to run a medical school, how to run a hospital, and how to make use of all the advantages of living in the age of the managerial revolution. It turns out to be no such thing, but a really very stimulating discussion of rather more general problems of social, sociological, humanitarian, and economic changes in the practice of medicine and the education for this practice. It also includes problems dealing with the numerous ancillary members of what seems now to be finally established as a team operation—the care of the sick. Naturally the problem of semantics occurs.

It is pleasant to note the rarity of barrages of the jargons which so often disfigure writings on this topic. Thus we find very few allusions to formulations, evaluations, coordinatings, personnel, level, coverage, integrations, facilities, and the like. This does not say that the reading is easy. One reason may be that the entire book is run off as one continuous conversation. Even the index is not quite adequate to help one find his way about. The crux of the matter is whether the physician as a specialist can recapture his ancient value to people as a physician and humanist and, if not, to what extent this may be made up by members of that vast company of nurses, nurses aides, assistants, social workers, psychologists, psychiatric social workers,

psychosomatists, cultural anthropologists, and sociologists who are now to some extent supplanting the personal physician just as in the past to some extent the physician supplanted the priest. No doubt it all goes back to the early stages in the education of those who would be physicians, and I doubt that the loss of a broad feeling for the humanities will ever be replaced by all possible studies in social science, teamwork, psychology, and economics.

It is far too much to ask a discussion group such as this to provide all the answers. It is enough that a grave problem has been recognized and that thoughtful questions have been raised in an intelligent fashion, for without this no solutions are possible. Whether or not one subscribes to the doctrines manifest in the approaches and answers that are given in this first conference on Administrative Medicine, at least the problem and its many ramifications is clearly defined. The question is asked. It remains to see what can be done about it.

1954 Medical Progress. Edited by Morris Fishbein, M.D. Price, $5.00. Pp. 345. The Blakiston Company, 575 Madison Ave., New York 22, 1954.

This excellent volume is a sign of the times, indicating the almost frantic efforts which are being made to review the vast literature and to help doctors keep up to date. We find here, in some 350 pages, excellent review articles on a variety of subjects, written by authorities such as Paul White, Charles Mayo, Frederick Stare, Perrin Long, and others. Obviously within these confines not too much can be said in detail, but that may be a virtue, as the writers have for the most part confined themselves to fairly fundamental considerations of general interest. This would certainly be a useful volume for any doctor to have on his desk as well as for pleasant reading. Each chapter is followed by a fairly comprehensive bibliography.

Disorders of the Blood. Seventh Edition. By Sir Lionel E. H. Whitby, M.D., and C. S. C. Britton, M.D. Price, $9.50. Pp. 856, with 20 plates and 106 text figures. Grune & Stratton, Inc., 331 Fourth Ave., New York 16, 1953.

The present revision of this popular British treatise on hematology continues to maintain the high values of previous editions and, as the authors modestly state, is, "a reasonable presentation of the subject to the middle of 1953." The text has been increased by 87 pages, largely through the addition of valuable chapters on biochemistry and cytochemistry and new methods in technique, although it appears that nearly every page has been revised with new and more material. As in former editions, the text is unusually conserving of verbiage, carrying a high ratio of pertinent information to print on every page.

The text progresses logically, beginning with the difficult and controversial subject of blood formation through the primary blood diseases to the blood changes secondary to various diseases and ending with 113 pages of technique. The 20 plates and 106 text figures are unusually good, and the index is most complete. All controversial subjects are treated conservatively and the various viewpoints fairly represented. The bibliographies that follow each chapter are well chosen. It is doubtful if there is a better book available on hematology for the internist.

Year Book of Drug Therapy 1953-1954. Edited by Harry Beckman, M.D. Price, $6.00. Pp. 538, with 70 illustrations. Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1954.

In these times of extremely rapid clinical progress compendia of current medical knowledge become a necessity for all physicians who make any pretense of keeping abreast of new developments. For the average internist and general practitioner the "Year Books" fill the need more adequately than any other summarized material with which the reviewer is familiar.

The present volume presents informative extracts on such subjects as the newer administration forms of penicillin, chloramphenicol, and oxytetracycline; isoniazid in tuberculosis; further data on the value and shortcomings of anticoagulants in myocardial infarction, with discussion of new drugs in this field; 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide (acetazoleamide; Diamox) as a substitute for mercurial diuretics; new antimalarial drugs, etc.

The editor, a man of long experience, has selected his material carefully and has commented wisely on new and controversial issues. The 1953-1954 Year Book of Drug Therapy is a worthy member of this useful series of abstracts.

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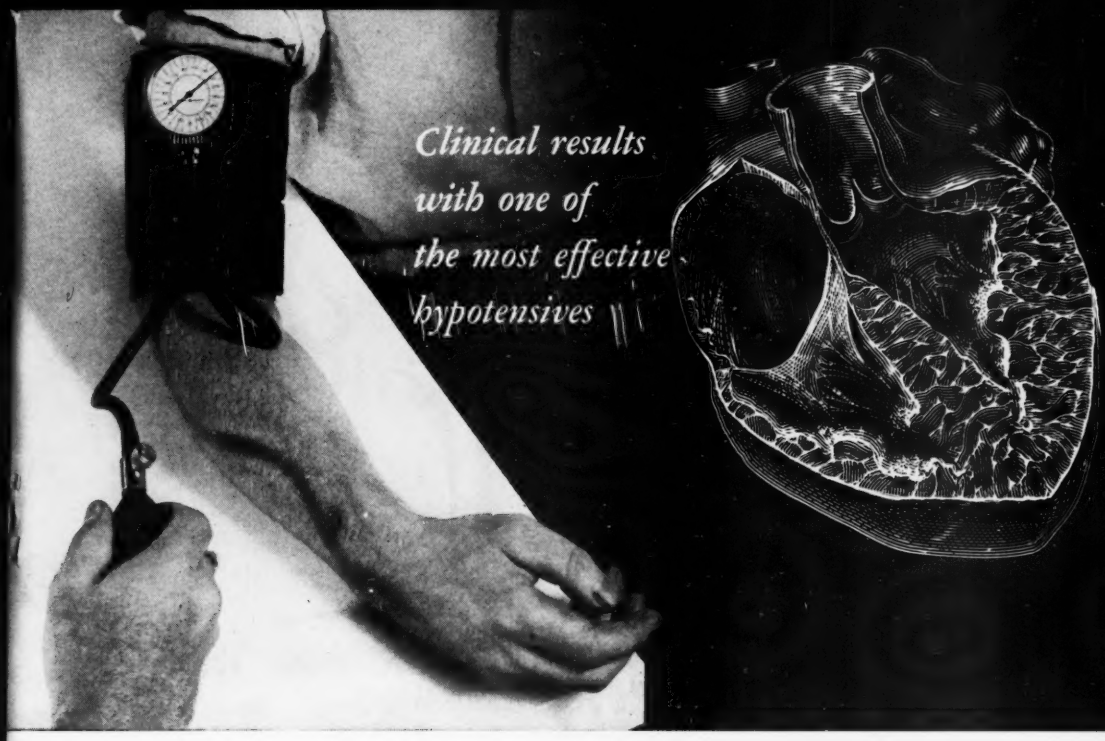

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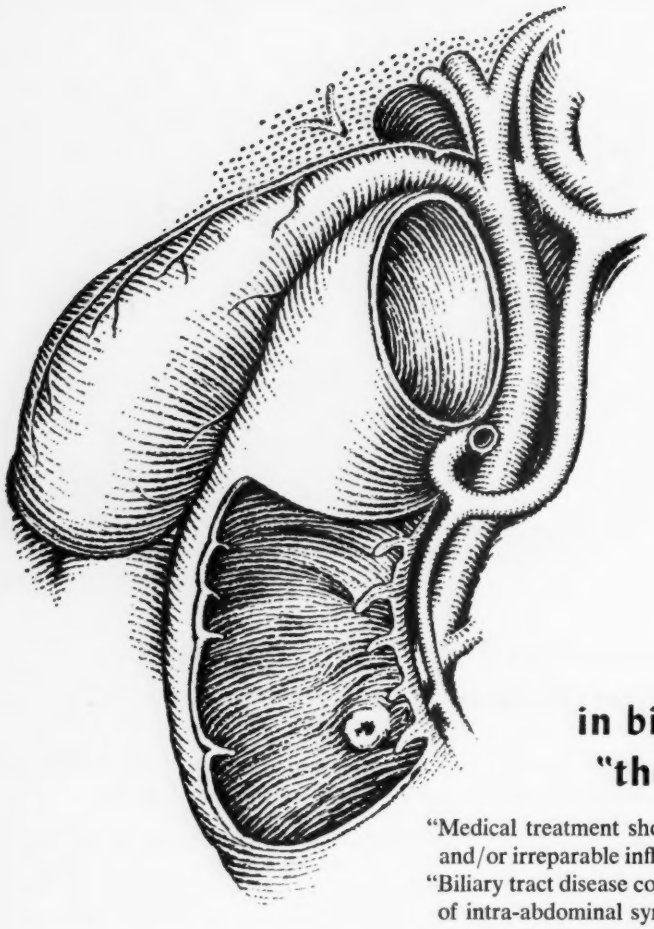

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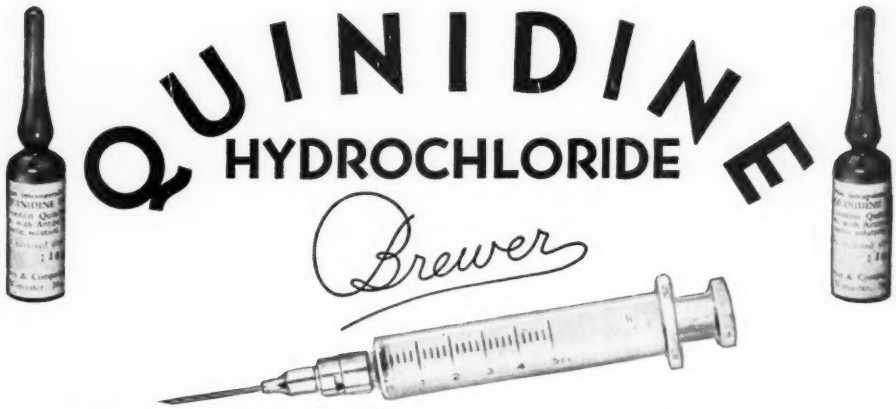

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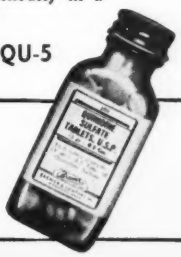

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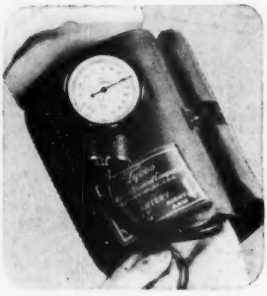

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